Malaria

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

Acknowledgments

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Disclaimer

The views expressed in this presentation are those of the speaker and authors, and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government

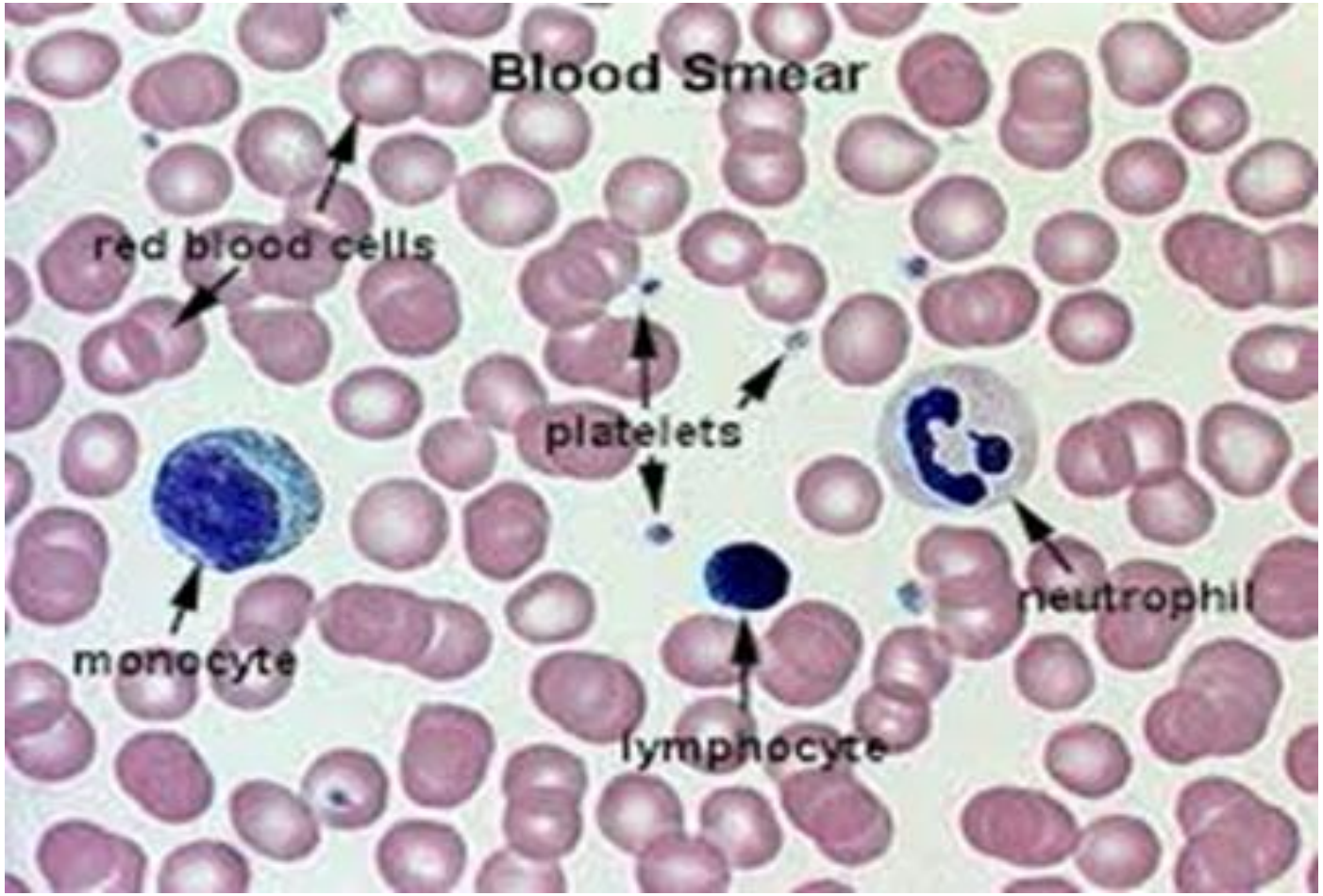
Case

- 23 y/o SM comes to your clinic in CONUS.
- Has had 3 days of chills, fever, sweats, nausea, vomiting, body aches, feeling unwell…
- Really doesn't want to bother you…but just wanted to come in to get checked out.

What questions do you ask?

Tests

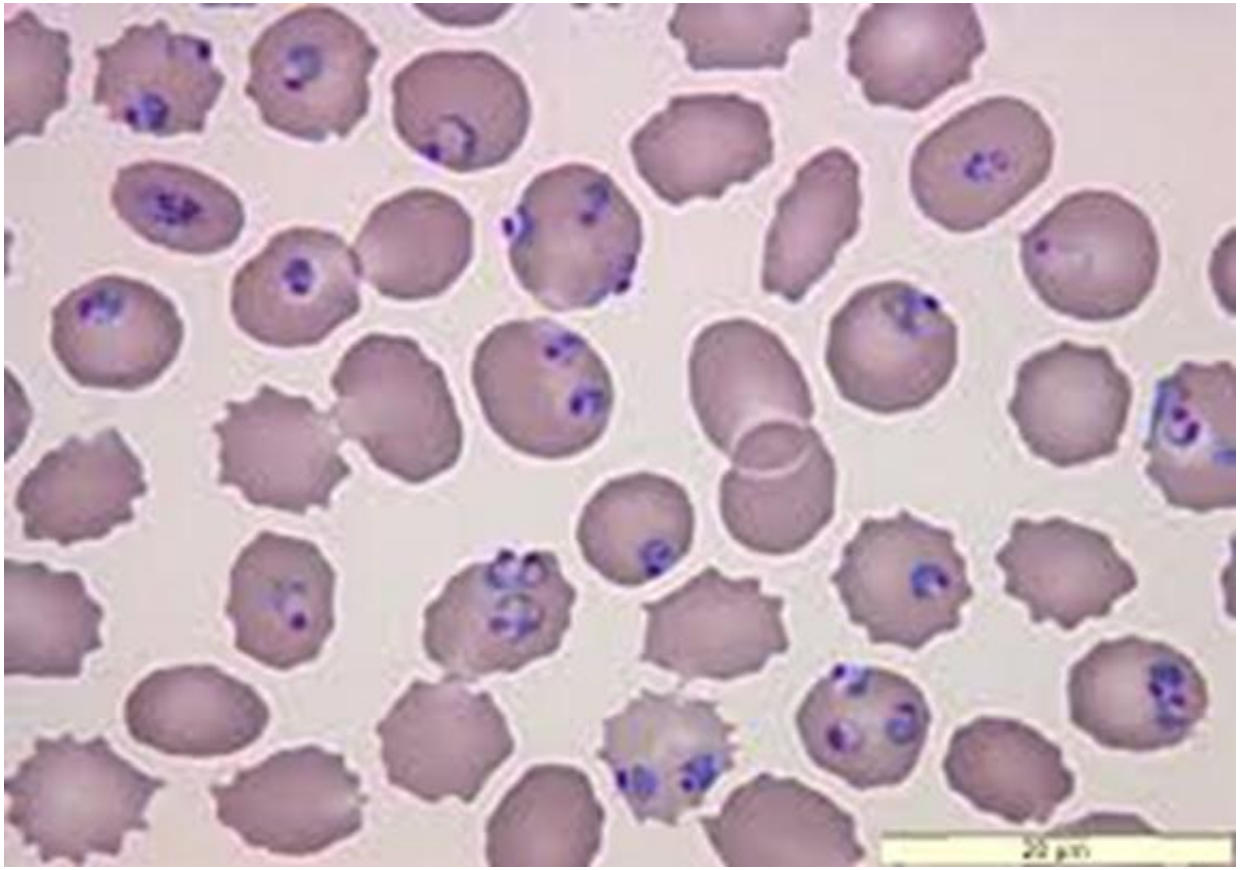
- **You ask:** “Where have you traveled in the last 6 months?”
- **Answer:** “Liberia, HOA, SE Asia.”
- You do a RDT…..negative
- You do a blood smear….


Blood Smear
red blood cells
platelets
monocyte
lymphocyte
neutrophil

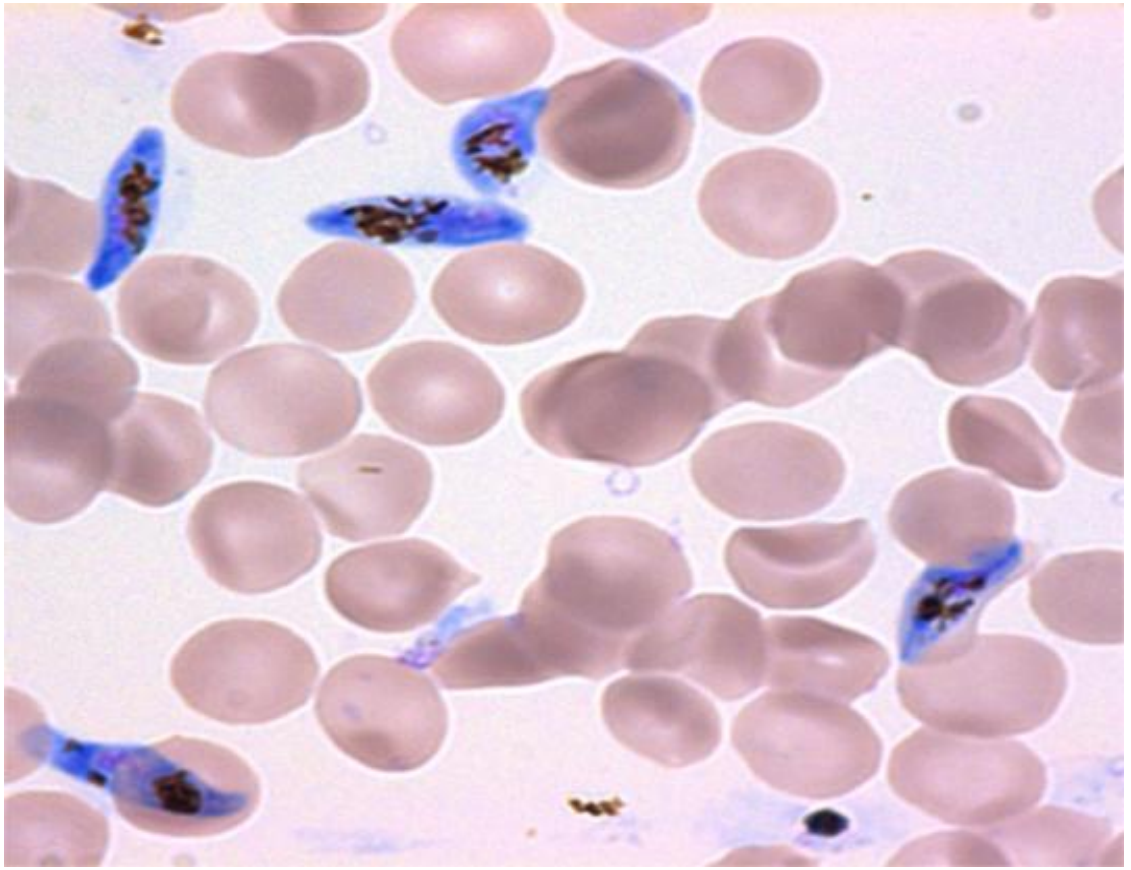
Later….

- He returns 2 days later
- He doesn't look too good
- On exam
  - VS: 103.3°F, 90/50, 120, 16
  - General: appears sleepy, oriented to name alone, diaphoretic
  - CV: tachycardic
  - Neuro: confused
  - GI: Hepatosplenomegaly, jaundice
  - Lab: Glucose: 20, HCT 15, Cr 2.6, AG 34
    - Should you be worried….very worried?

Now: You see this in the blood smear….



Source: http://news.psu.edu
http://imgkid.com



Source: http://news.psu.edu
http://imgkid.com

Overview

- Malaria is a complex, large global problem
- Current strategies are inadequate
- DoD is making progress towards malaria solutions (drugs and vaccines)
- Multi-pronged efforts are ongoing in the areas of malaria control, elimination, and eradication.

What is Malaria?

- Potentially lethal parasitic disease (*Plasmodium* species)
- Transmitted between humans (reservoir) by mosquitoes (the vector)
- **Initial malaria**: fever, chills, muscle aches, headaches, fatigue, rigors

  → **ACUTE ILLNESS**
- **Untreated**: severe anemia, kidney failure, coma, convulsions

  → **DEATH**

  
- **Survivors**: May become chronic carriers (esp. *P. vivax*)

  → **ILL HEALTH, LEARNING DISABLED**

  → **RESERVOIRS OF INFECTION**

History

- Chinese writings (2700 BCE)
- The Eber's papyrus (1550 BCE)
- Hippocrates (described malaria fevers)
- Greek civilizations affected by "bad air", the rich summered in the highlands
- Malaria in the United States
  - First military expenditure in 1775 ($300) for quinine to protect Washington's troops
  - In Civil War (1861-65) 50% white and 80% of black troops w/ malaria annually

Ancient Roman bones reveal malaria

ROMAN from Page 2A

skeletal remains."

Dr. David Soren, a classical archaeologist at the University of Arizona in Tucson, praised the DNA results as "new and really exciting" because "the idea that this deadly type of malaria really existed in imperial Rome had never been documented."

An international team led by Soren excavated the children's cemetery in the early 1980s and discovered more than 50 small skeletons. Most of them, found in earthen jars, were the remains of stillbirths and early infant deaths. The falciparum parasite is known to cause aborted fetuses and infant mortality. A few of the older skeletons had porous and pitted cranium surfaces, which can be the result of an infectious disease like malaria.

This and considerable circumstantial evidence led Soren to the hypothesis that malaria epidemics might have had grave consequences on Rome. Scientists at the University of Rome have found evidence showing that falciparum malaria came from Africa, underwent mutations in Sardinia and was introduced in the marshy, mosquito-infested Tiber River basin by the fifth century.

Dr. Frank Romer, a Roman historian at Arizona, noted accounts of pestilence spreading through the countryside at this time and causing "sweats and chills," symptoms typical of malaria. It was in 452, a year or two after the infant burials, that Attila, marching toward Rome, suddenly decided against entering the city.

If the DNA tests have indeed linked the infant deaths to malaria and not some other causes, Soren said he hoped other archaeologists would take notice and begin to incorporate biomolecular research in their investigations.

"I think in 10 or 15 years, this will come to be standard practice in archaeology," he said. "We need not just excavate bones and throw them into a closet. We need to take those bones and make samples for DNA testing."

The Situation is Dire

- Malaria is a personal tragedy
  - Death in infants and in 1st pregnancies
  - Sickness, long term disability, chronic illness in survivors

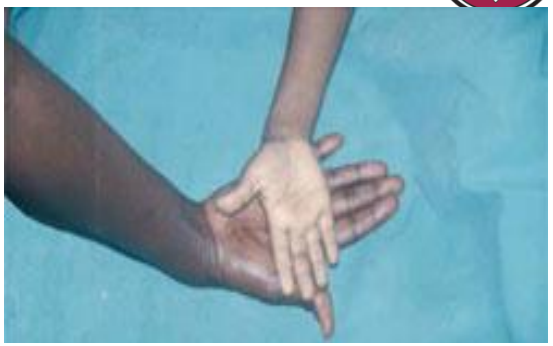
- Malaria is a global health tragedy
  - Malaria kills 3,000 children a day
  - Malaria hastens spread of HIV infection**

- Malaria is an economic-political tragedy
  - Major cause of disability adjusted life years (DALYS)
  - Prevents development, especially in Africa
  - A cause and a consequence of poverty

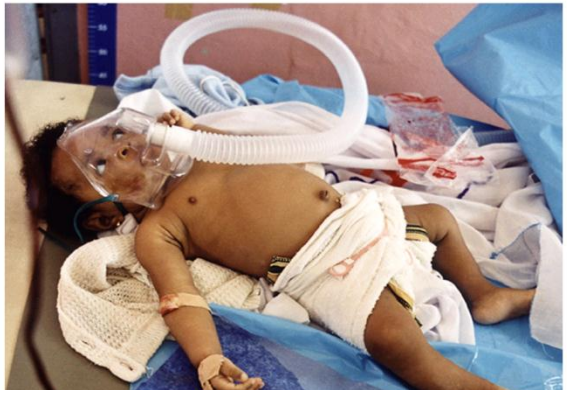
**Abu-Raddad LJ et al. Links Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 2006;314:1603-6

The Global Malaria Problem

- #1 cause of death of young African children
- Malaria is resurgent:
  - More cases now than ever in history
- Inadequate prevention:
  - Bed nets save lives - but not widely used
  - DDT/insecticides save lives – but not adequa
- Inadequate treatment
  - Poor diagnosis
  - Drug resistance:
    - affordable drugs not effective
    - effective drugs not affordable
- No malaria vaccine yet licensed

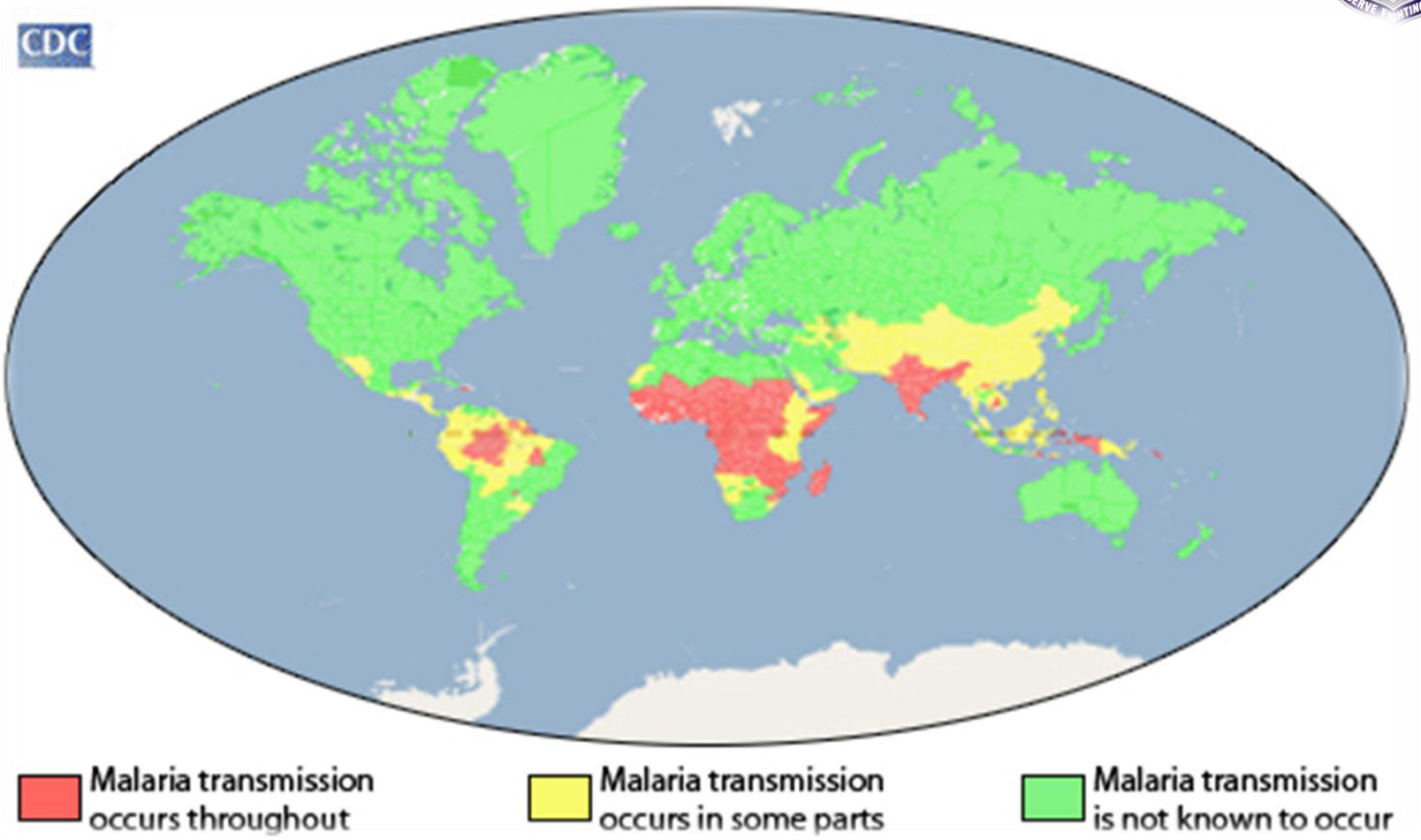


Hand of child with severe malaria anemia in the palm of his mother

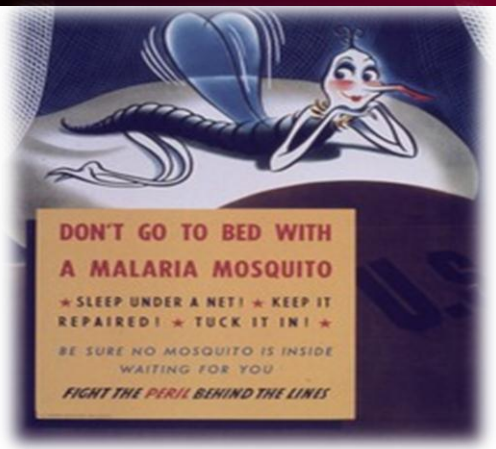


Child with severe malaria

Source: www2.cedarcrest.edu



Source: cdc.gov



Destabilization Effect

- Malaria (and other diseases) impact critical infrastructures
  - Education, health systems
  - Economic growth
  - Law enforcement, military, politics, family structures
- Disease undermines already weakened nations
  - Vulnerable to extremists/terrorists
- Real global war
  - Needs to be comprehensive
  - Fought on many levels
  - Many fronts

Malaria and Morbidity in the US Military

WWII	1939–1945	600,000 cases mostly in Pacific theater. In some areas of South Pacific malaria rates were 4 cases per person per year
Korean War	1950–1953	Malaria rate 611/1000/year; 3000 cases in troops returning to US
Vietnam War	1962–1975	100,000 cases, Hospital admissions 27/1000/year 1970: 2222 cases (mostly *P. vivax*) treated in United States
Somalia	1992–1994	48 cases; 243 cases in forces on return home (*P. vivax*)
Nigeria	2001	Special forces 7/300 (2 deaths)
Afghanistan (OEF)	2001-	Over 400 cases since 2005

Source: en.wikipedia.org

"Doctor, this will be a long war if for every division I have facing the enemy I must count on a second division in hospital and a third division convalescing from this debilitating disease!"

General Douglas MacArthur, May 1943 to Colonel Paul F. Russell, MC, the American Army malaria consultant.

Operational Impact - Liberia, 2003

- 80 of 220 (36%) Marines contracted *P. falciparum* malaria
- 46 required medical evacuation
- 5/80 (6.25%) were severe
  - Requiring ICU admissions
  - Four on ventilators
- Key problems:
  - Non-compliance
  - Inability to make the diagnosis
  - Cost: $1.2M

Vector: Anopheline Mosquitoes

Source: news.softpedia.com

- 50->80 species capable of transmission
- <40 responsible for majority of transmission
- Female requires blood meals for egg broods

Anopheline Mosquitoes

- Life cycle – 7 to 20 days (egg to adult)
  - egg -> larva -> pupa -> adult
  - Females mate once and lay 200-1000 eggs in 3-12 batches over a lifetime
  - Find their host by chemical (CO_2) and physical stimuli (heat)
    - Smokers
  - Average life span of mosquito < 3 weeks

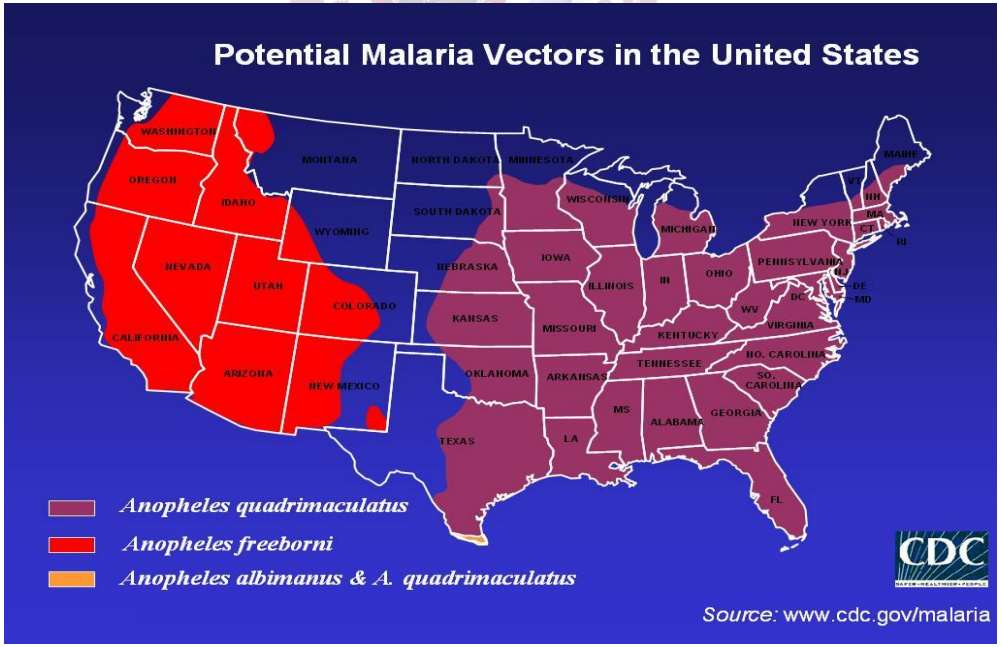
- Malaria development – 7 to 12 days
  - Each male & female gametocyte produce >10,000 sporozoites

Transmission

- Tropical and subtropical areas
  - Sub-Saharan Africa, India, Oceania considered endemic areas
  - Does not occur in all parts of endemic countries all the time (deserts, high altitude, cold seasons)
- Transmission-favorable factors
  - Anopheles mosquito niche
  - Temperature (CRITICAL)
    - Below 20°C (68°F), *P. falciparum* cannot complete growth in the mosquito → no transmission
    - The warmer the region, the more intense/constant transmission is

Transmission

- Temperate areas (e.g. Western Europe, USA) have eliminated malaria
  - Economic development
  - Public health measures
- Reintroduction is a constant risk



Transmission in the US

- Mosquito-borne
- “Airport” (imported mosquitoes)
- Congenital
- Transfusion
  - 1 year deferral
    - Donors who traveled to an endemic malarious area who remain free of symptoms for 1 year
  - 3 year deferral
    - Donors who lived in endemic malarious area who remain free of symptoms for 3 years after leaving
    - Donors with malaria diagnoses need to be asymptomatic for 3 years after becoming asymptomatic

Vector Websites

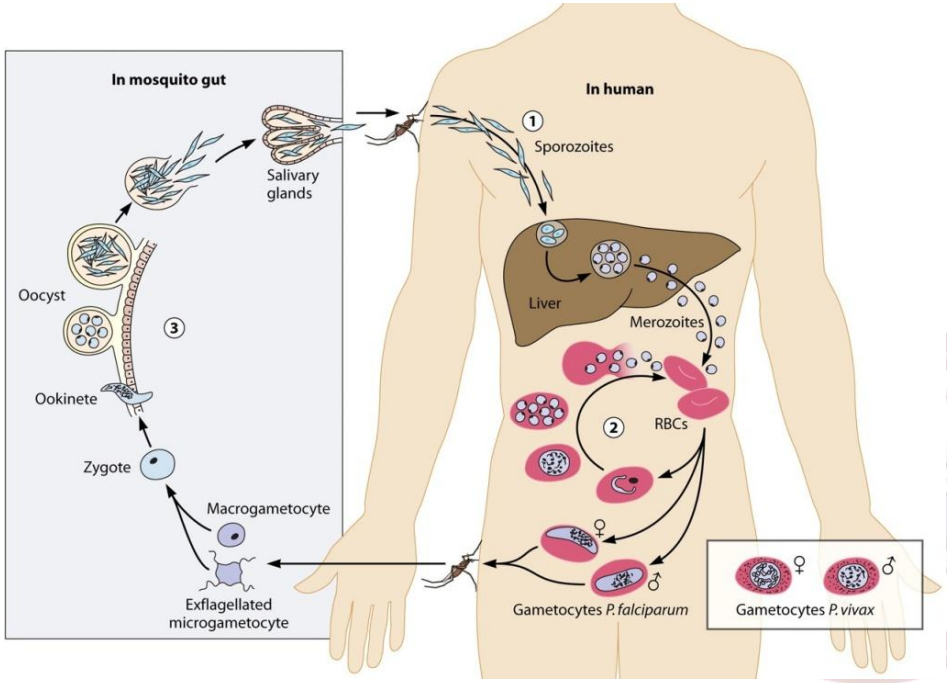
VectorMap

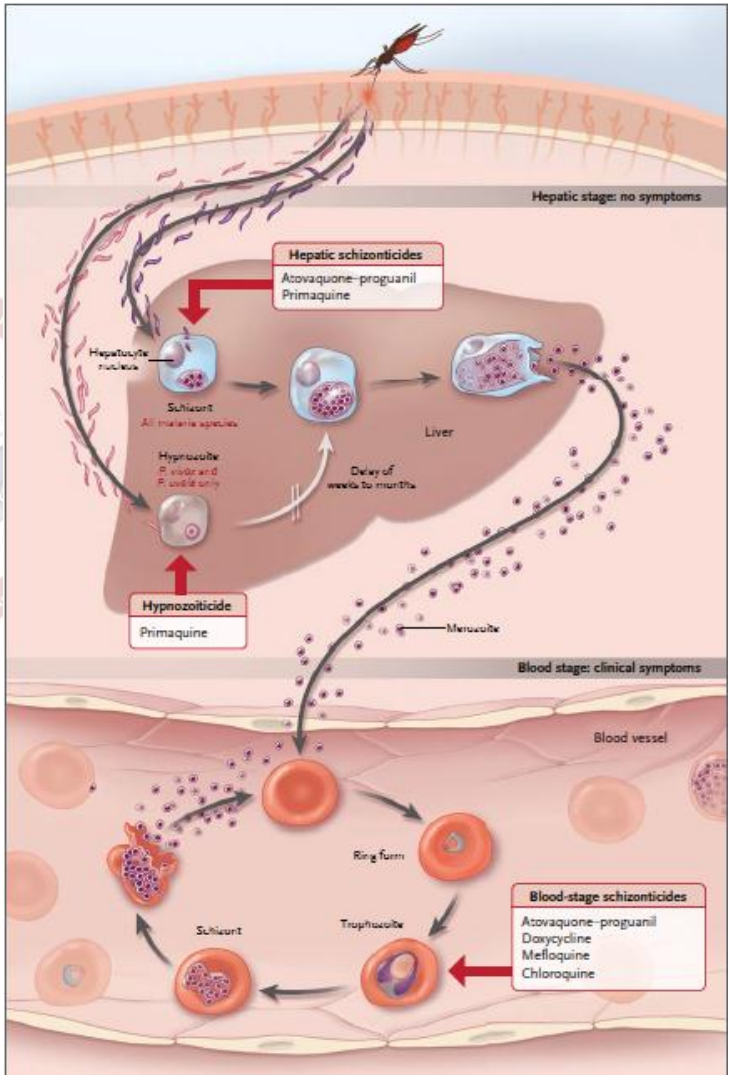
Know the vector, know the threat

MosquitoMap

http://www.vectormap.org/

Malaria Life Cycle





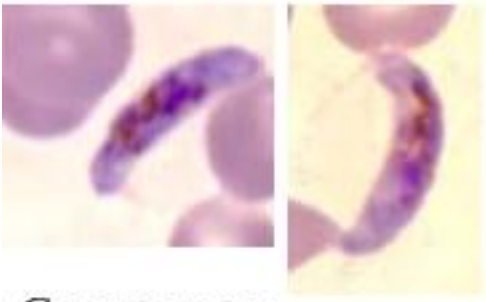
Key Point: most blood-stage schizonticides are suppressive—this is why prophylaxis is continued upon redeployment

Source: NEJM

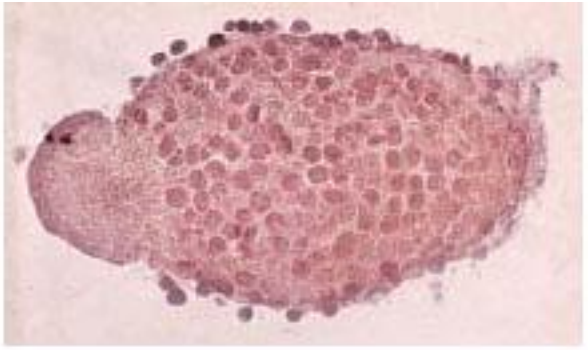
Plasmodium Life Cycle

Definitive host mosquito

Ingests 3 ul of blood
With 100-300 gametes



Gametocytes
Viable for 28 days



Oocysts on gut wal

28 days
In mosquito

100's

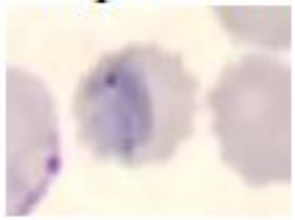
Sporozoites

Within hours invades 1-2 liver cells

1,000's released

Merozoites in liver for seven to 10 days. P. vivax & ovale hypnozoite for Months.

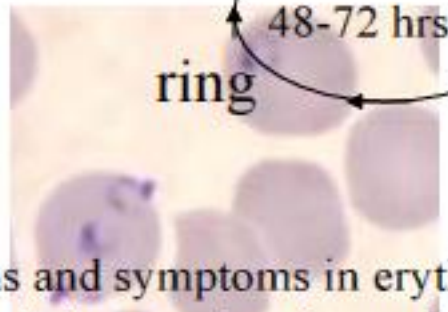
trophozoite



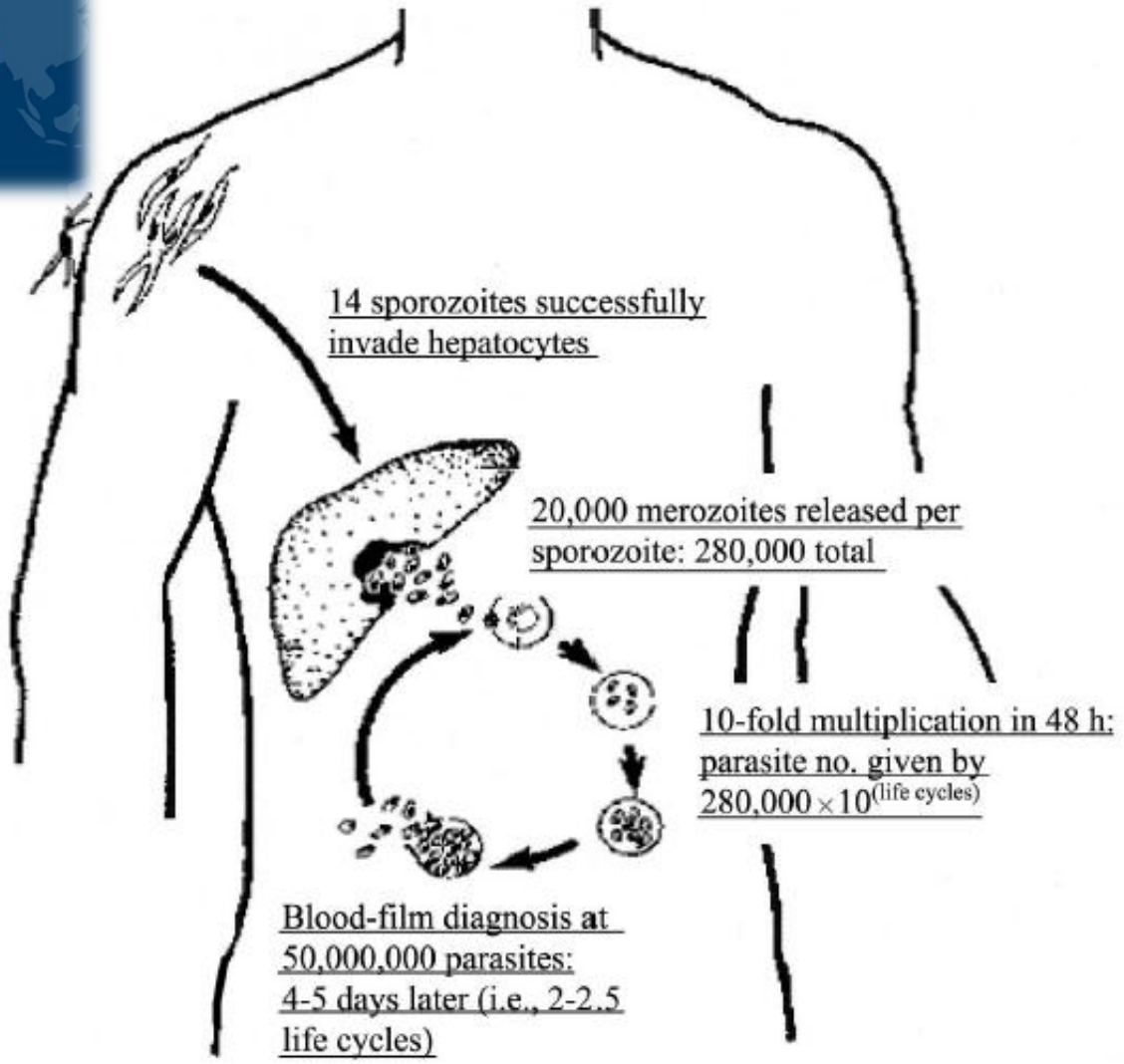
schizont

48-72 hrs

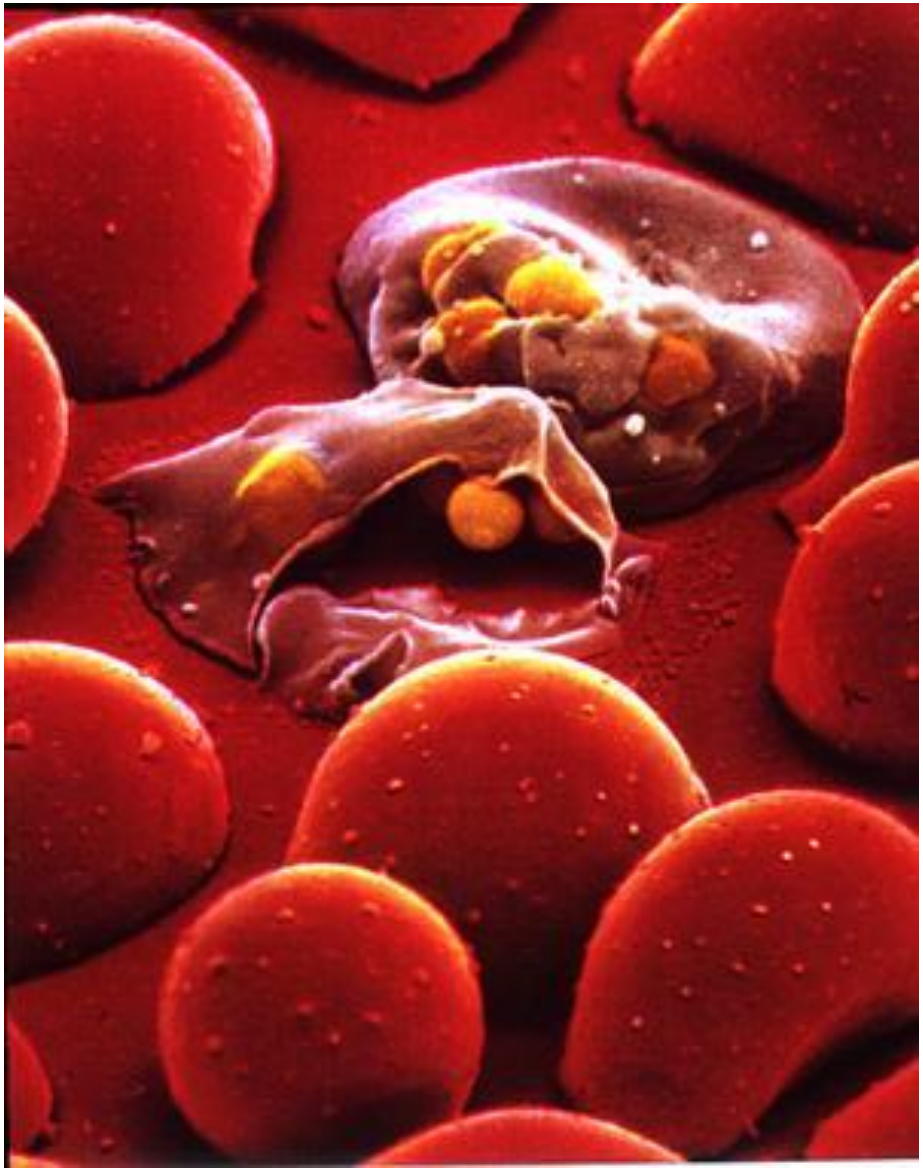
ring



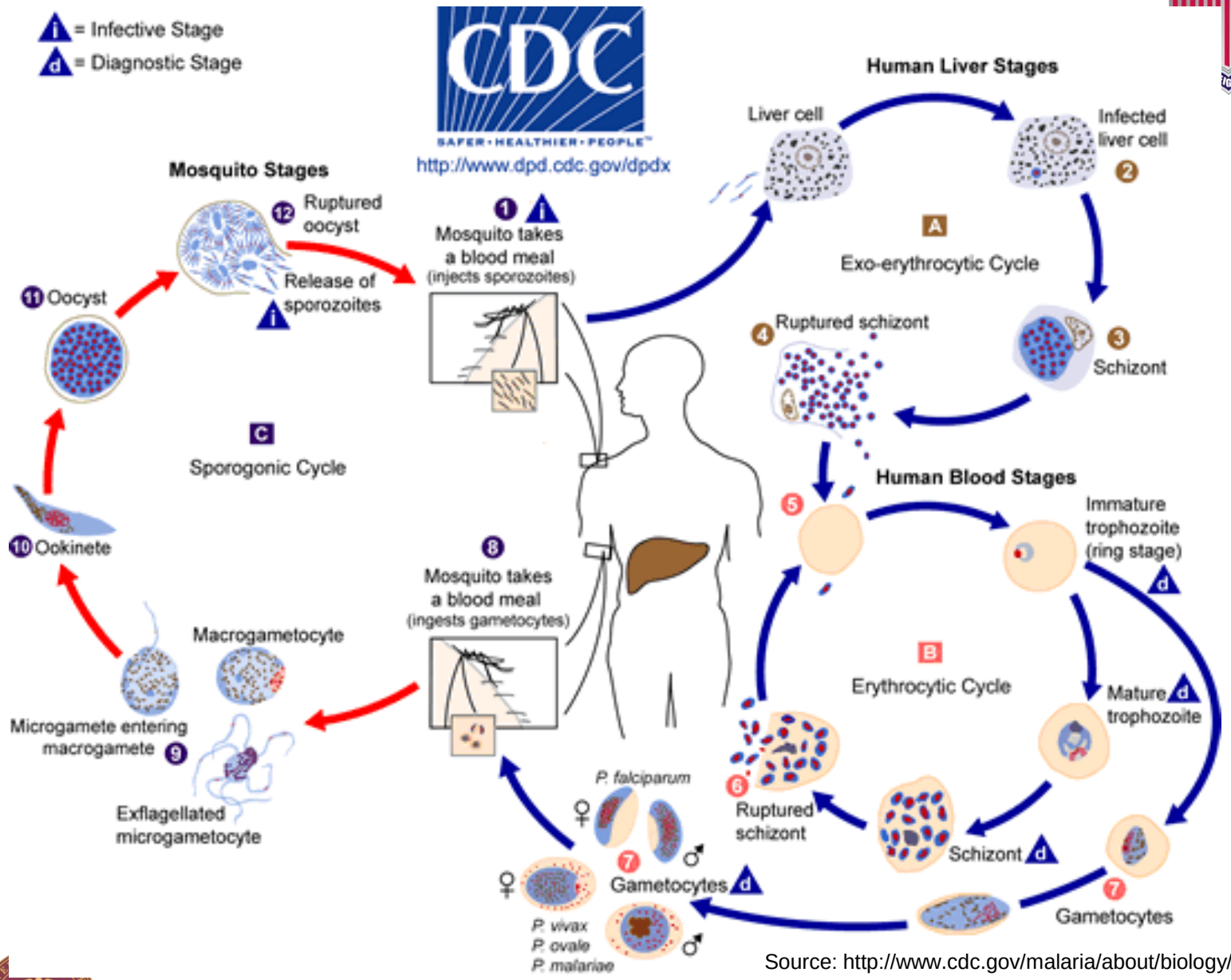
Clinical signs and symptoms in erythrocytic stages of ring,trophozoite and schizont



Source: JID 2005;191:625



Source: http://www.phsource.us/PH/HELM/PH_Parasites/Malaria.htm



Source: http://www.cdc.gov/malaria/about/biology/

Malaria Parasites and Their Life Cycles

- Five human forms of malaria
  - *Plasmodium vivax* (benign “tertian”)
    - 48h cycle, young RBCs (reticulocytes), worldwide
  - *Plasmodium malariae* (“quartan”)
    - 72h cycle, older RBCs, worldwide
  - *Plasmodium ovale* (“ovale tertian”)
    - 48h cycle, young RBCs, Africa
  - *Plasmodium falciparum* (“malignant tertian”)
    - 24-48h cycle, all RBCs, Tropical regions
  - *Plasmodium knowlesi*
    - 24h cycle, probably all RBC’s, Southeast Asia (Malaysia/Indonesia/Borneo)

“Recurrent Infections”

- Relapse
  - Hypnozoite stage of *P. vivax* and *P. ovale*
  - Months or years later
  - May be impossible to completely prevent
- Recrudescence
  - Incomplete treatment or partially effective host immune responses
  - Most frequent *P. falciparum*- due to drug resistance
- Reinfection
  - Most frequent with *P. falciparum*- intense transmission

Source: CAPT Claggett, USN

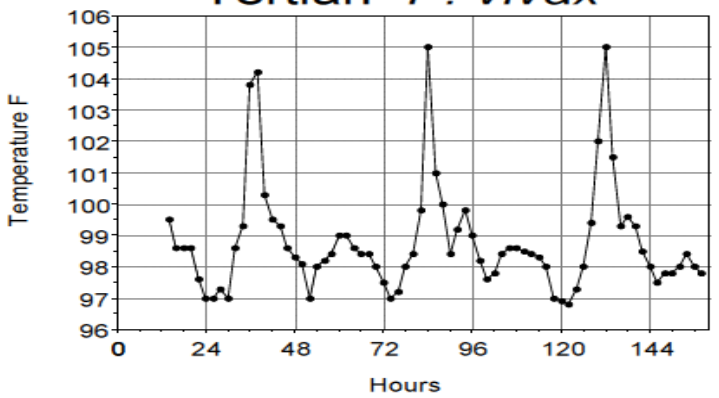
Symptoms/Signs

- Incubation period 7-30 days
- Classical malaria attack lasts 6-10 hours
  - Cold stage (sensation of cold, shivering)
  - Hot stage (fever, headaches, vomiting; seizures in young children)
  - Sweating stage (can be diaphoretic, more commonly a combination of fever, chills, sweats, headaches, nausea and vomiting, body aches, malaise.)
- Physical findings
  - elevated temperatures, sweating, weakness, enlarged spleen, mild jaundice, hepatomegaly, tachypnea

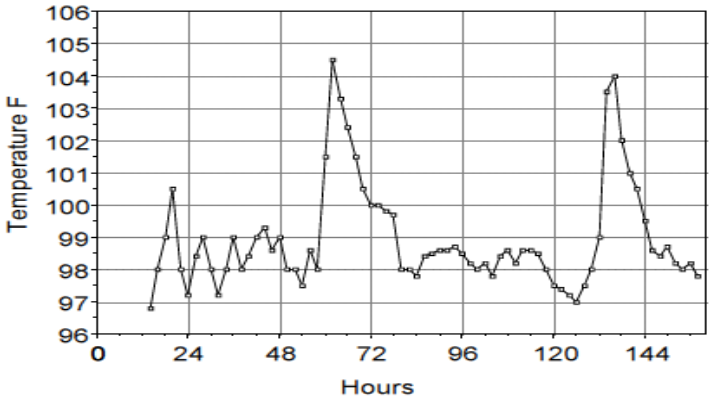
Comparison of Malaria Fever Curves

Adapted from Thayer and Hewetson
Johns Hopkins Hosp Reports V 1895 p. 3-224

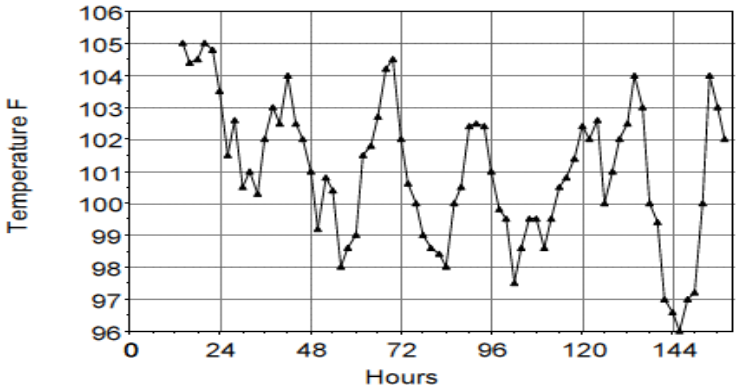
"Tertian" *P. vivax*



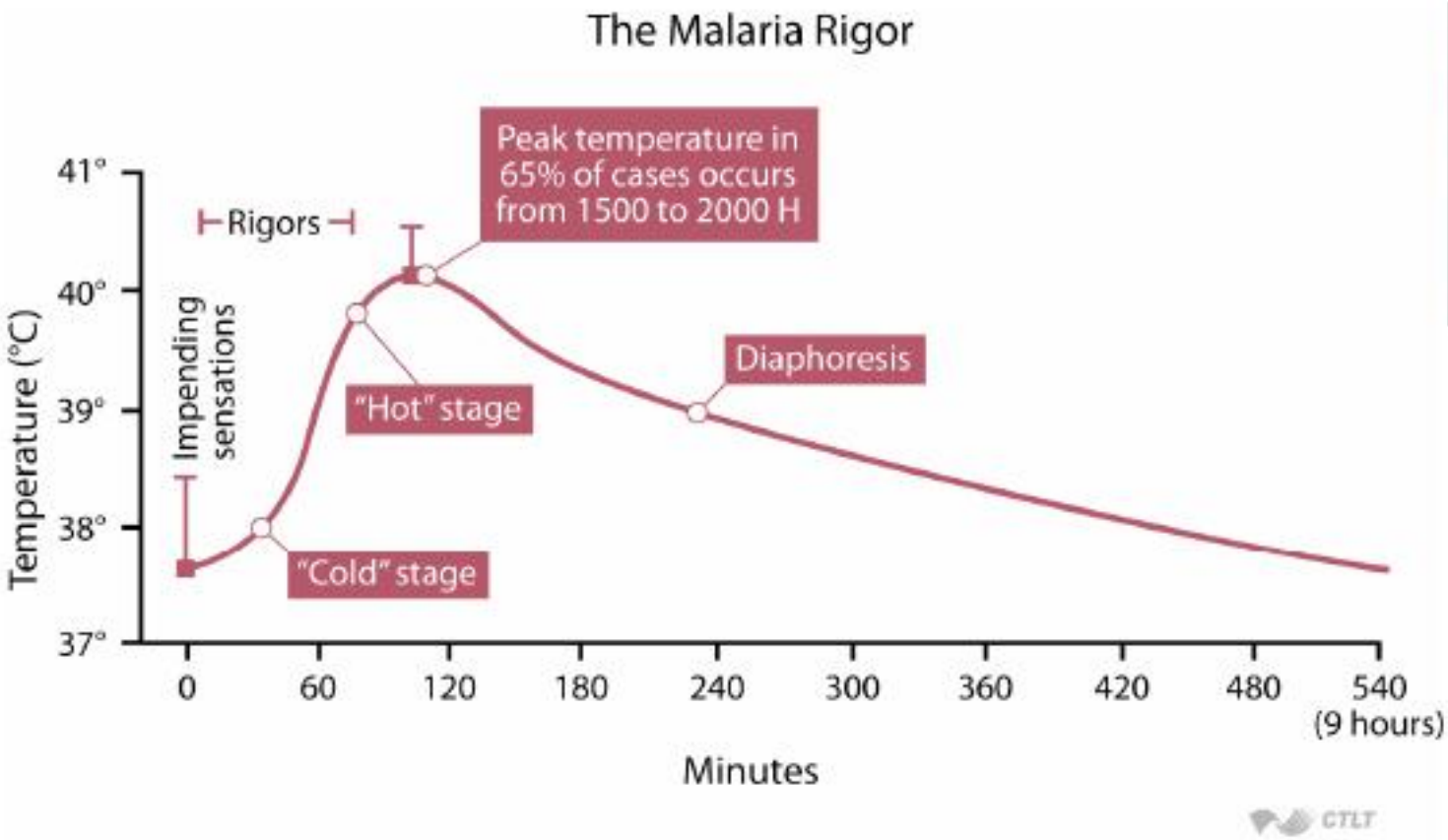
"Quartan" *P. malariae*

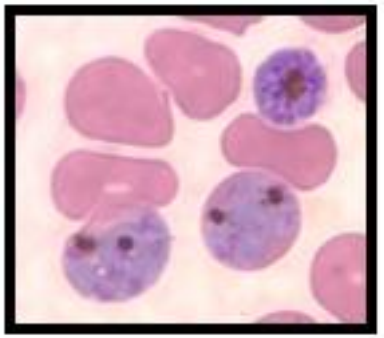


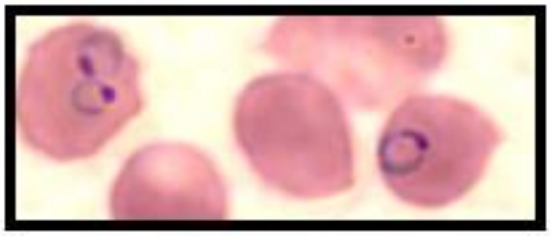
"Aestivo-autumnal "Quotidian" *P. falciparum*



Classically (but infrequently observed) the attacks occur every second day with the "tertian" parasites (*P. falciparum, P. vivax,* and *P. ovale*) and every third day with the "quartan" parasite (*P. malariae*).







Pyrogenic density is parasite density at time of fever.
P. vivax pyrogenic density is 100 parasites /µl
P. falciparum pyrogenic density ranges from 0 to 10,000/µl in nonimmunes
Semi-immune can have up to 100,000 par/µl without fever

Plasmodium knowlesi

- BLUF: Nasty one
  - Looks like a benign species, but as deadly as Pf.
- Simian species of malaria naturally infecting macaques in Southeast Asia
  - Human cases reported first in Borneo
  - Subsequent cases in Malaysia, Singapore, and Philippines
- Resembles human species by microscopy
  - *P. malariae* (affects any age cell like *P. falciparum*)
- 24 hour replication cycle
  - Can cause severe and fatal infections

Severe Malaria

Severe malaria is a medical emergency and should be treated **urgently and aggressively.**

Multi-organ failures or abnormalities in the patient's blood or metabolism.

Severe Malaria

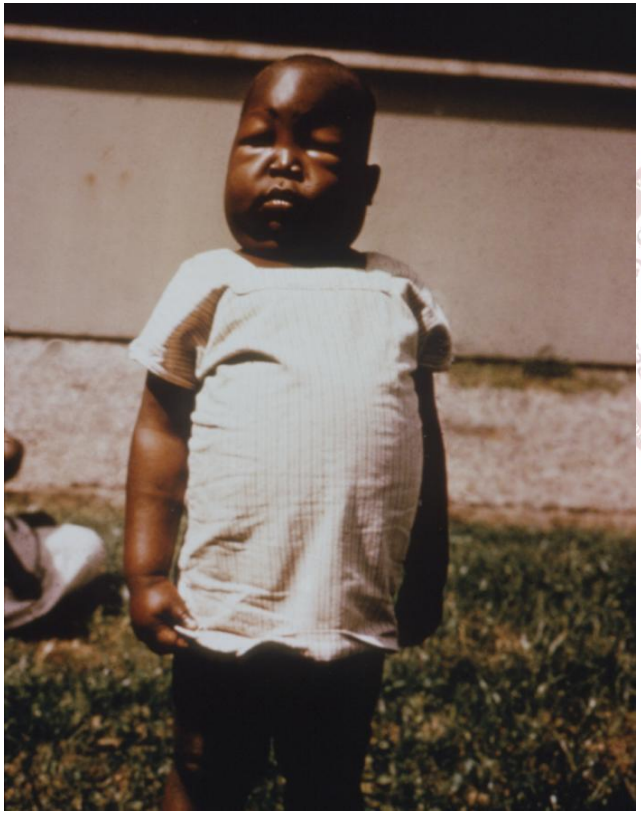
- Cerebral malaria
- Severe anemia due to hemolysis
- Hemoglobinuria due to hemolysis
- Acute respiratory distress syndrome, can even after patient is responding to treatment
- Abnormalities in blood coagulation
- Low blood pressure caused by cardiovascular collapse
- Acute kidney failure
- Hyperparasitemia (>5% RBCs)
- Metabolic acidosis
- Hypoglycemia (can also occur in pregnant women with uncomplicated malaria, or after treatment with quinine)

Clinical Complications of Malaria

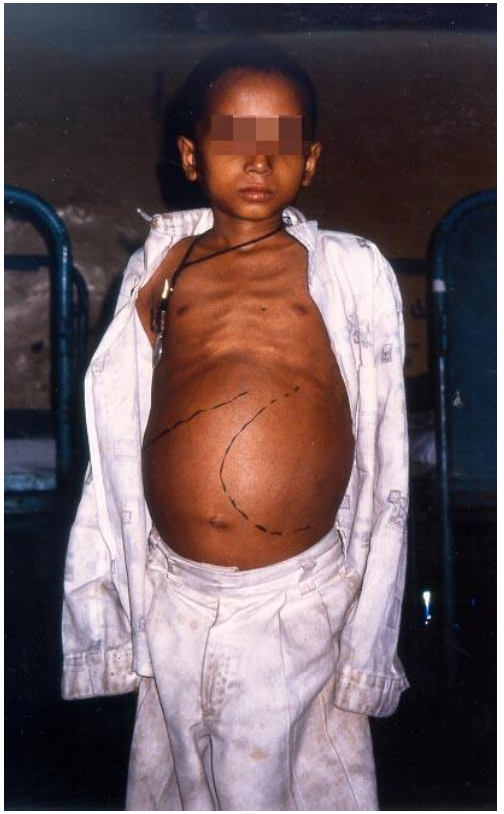
- *P. falciparum*
  - *Cerebral coma (kids)*
  - *Anemia (s/p recurrent)*
  - *Pulmonary Edema*
  - *Renal Failure*
  - *Shock*
  - *Lactic acidosis*
  - *Hypoglycemia*
  - *Tropical splenomegaly syndrome*
    - *Hepatosplenomegaly, anemia, skin/respiratory infections*
  - *Pregnancy*
    - *Maternal death*
    - *Stillbirth*
    - *Low birth weight*
    - *Anemia*
- *P. vivax (ovale)*
  - Splenic rupture
  - Anemia (mild)
  - Debilitating fever
  - Higher TNF-α per parasite
- *P. malariae*
  - *Immune complex*
  - *Glomerulonephritis → nephrotic syndrome*

Malaria Complications

- Nephrosis/Edema



- Tropical splenomegaly
  (Hyperreactive Malarial Syndrome)



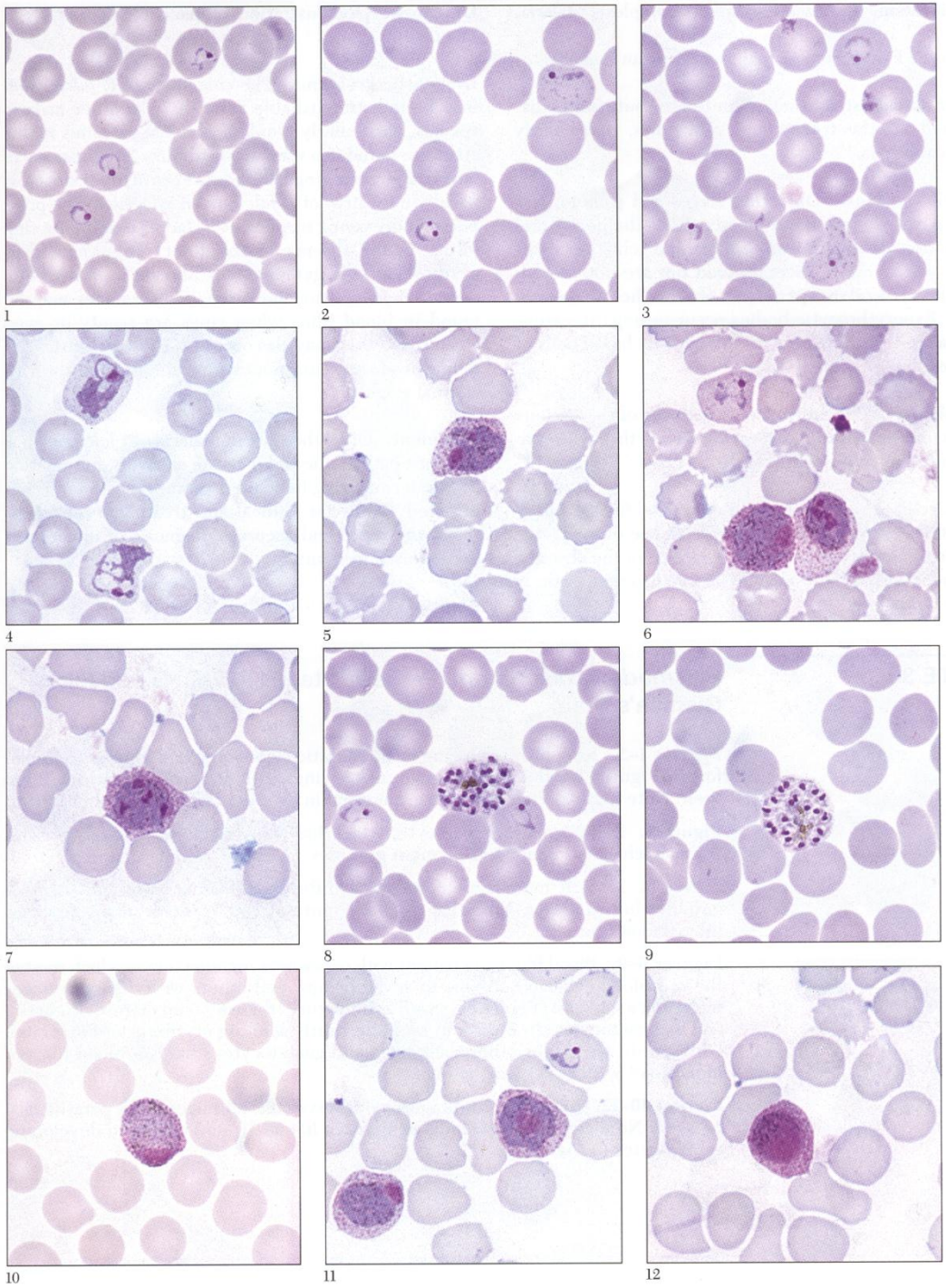
Source: www.encyclopedia.com
Emedicine.medscape.com

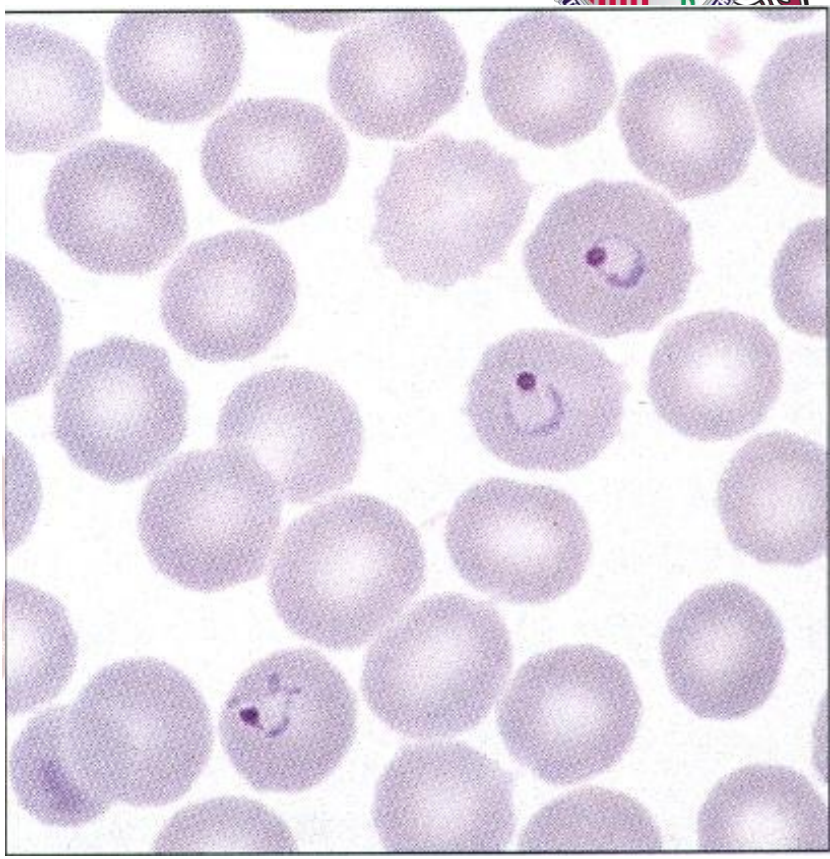
Diagnosis

- Gold standard – Giemsa thick & thin smears
  - Species and parasite density determined
  - Labor intensive, modest cost
  - False negative circumstances
    - Parasites not present in circulation (“Sequestration”): *P. falciparum*
  - False positive circumstances
    - Parasites seen may not be the cause of fever in endemic areas – bacteremia (prominently Salmonella sp.) common
  - In highly endemic areas, clinical diagnoses made
  - http://www.dpd.cdc.gov/dpdx/Default.htm

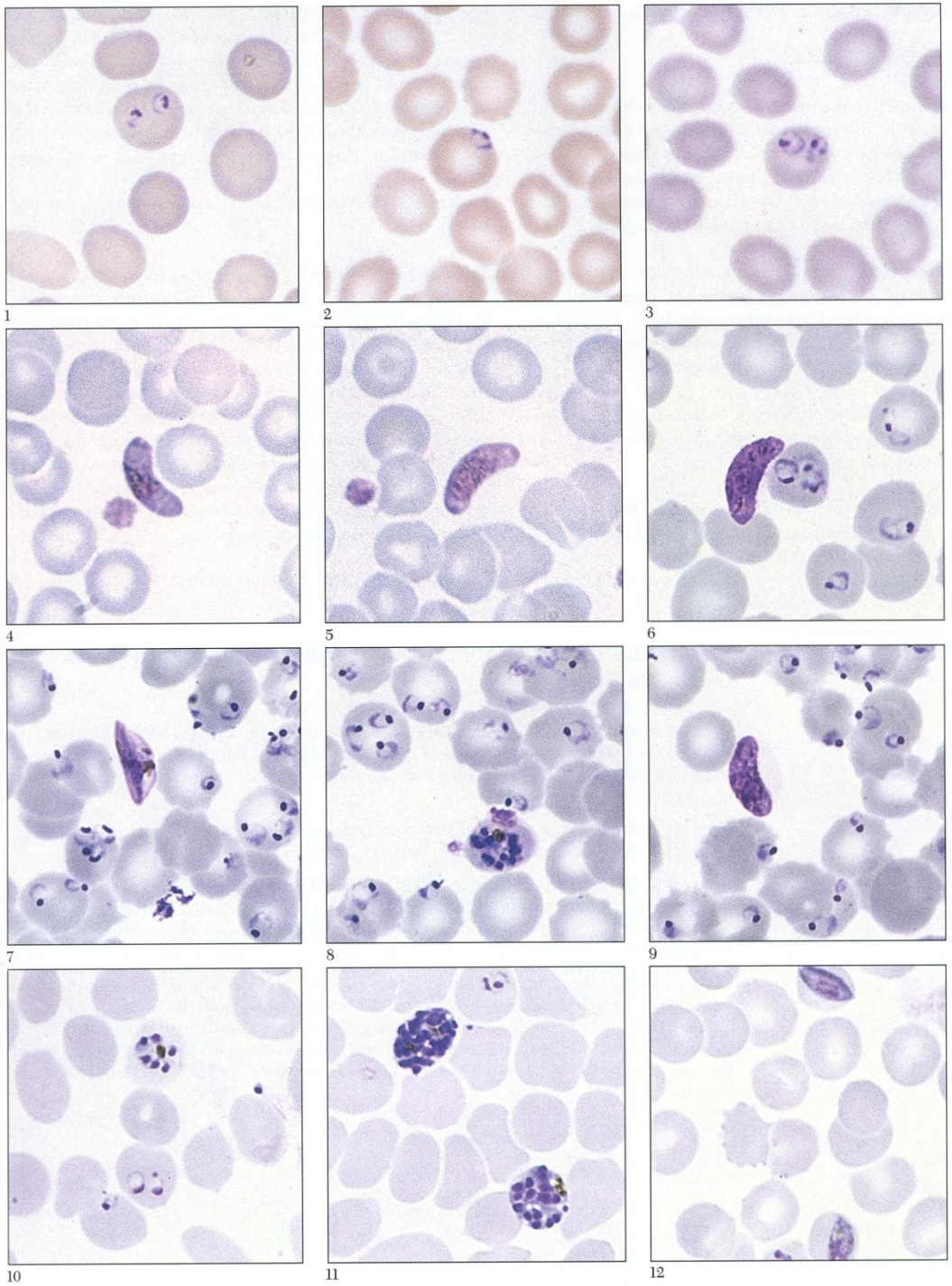
Levels of Parasitemia in Different Patient Groups

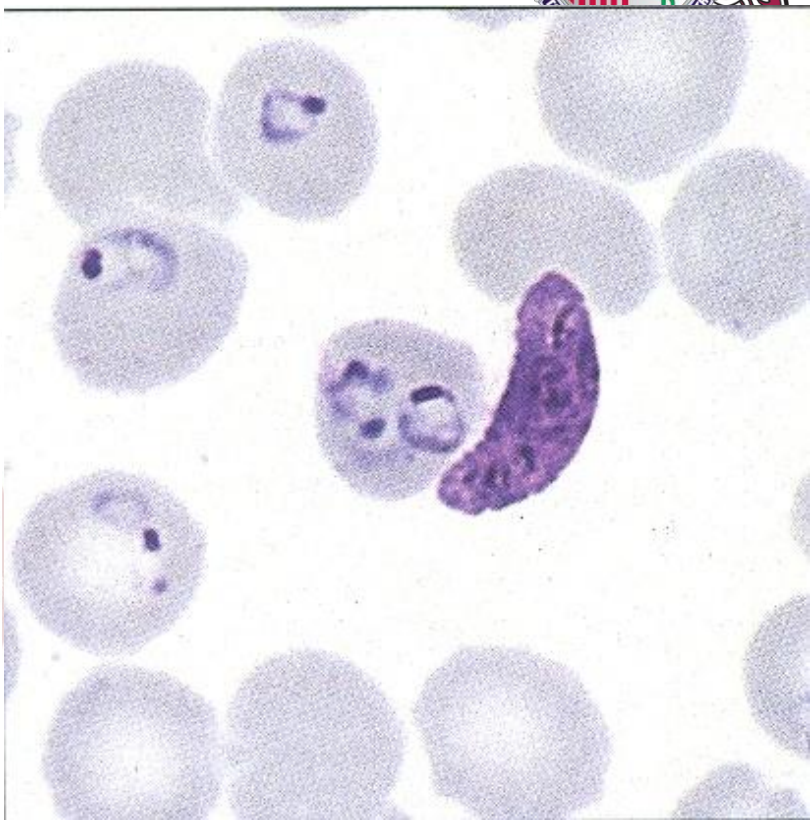
	Parasitemia	Parasites / µL of blood
Positive thick smear	0.0001-0.0004%	5-20
Naïve patients with symptoms (below this level)	0.002%	100
Emergency room patients and travelers	0.2%	10,000



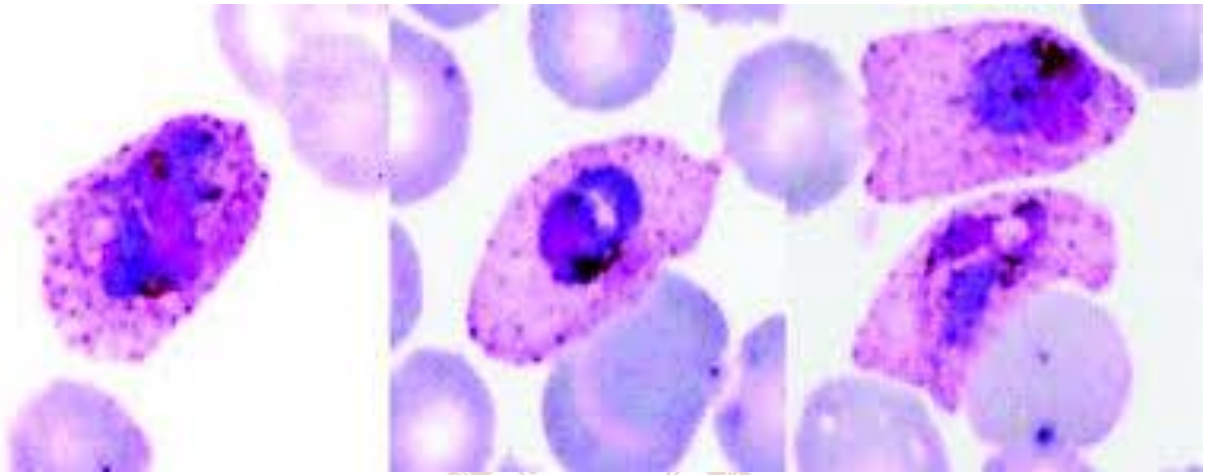


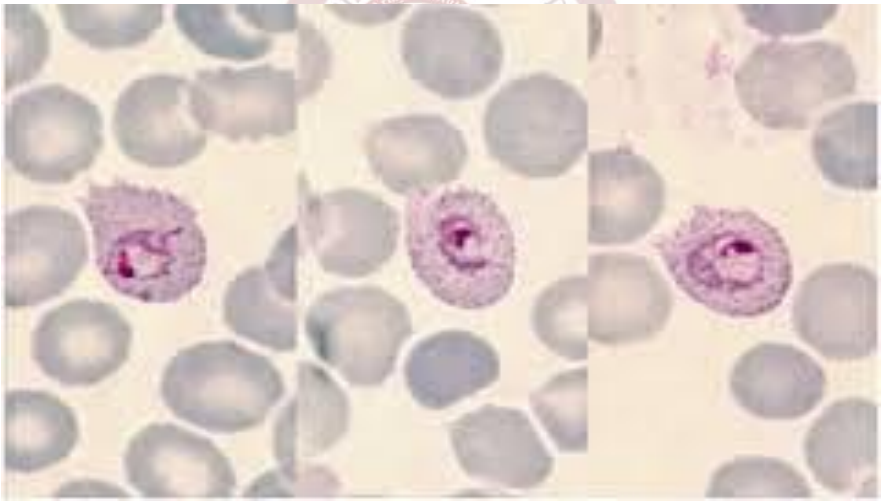
Plasmodium vivax



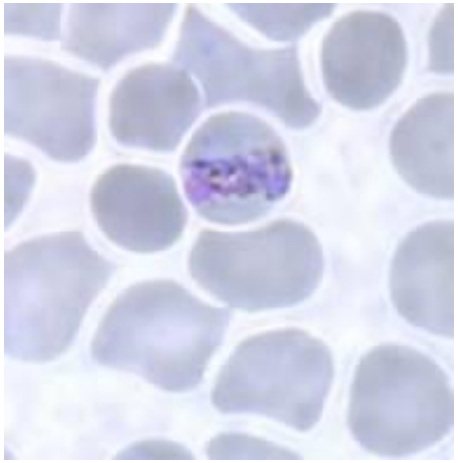


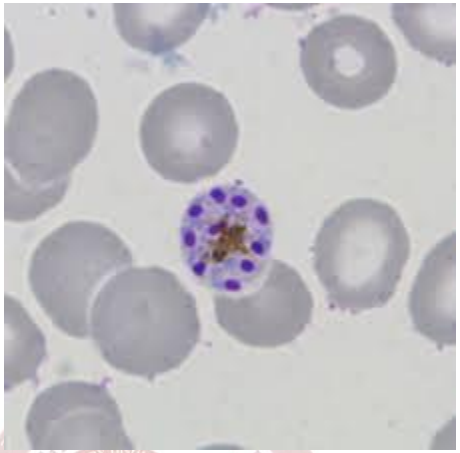
Plasmodium falciparium

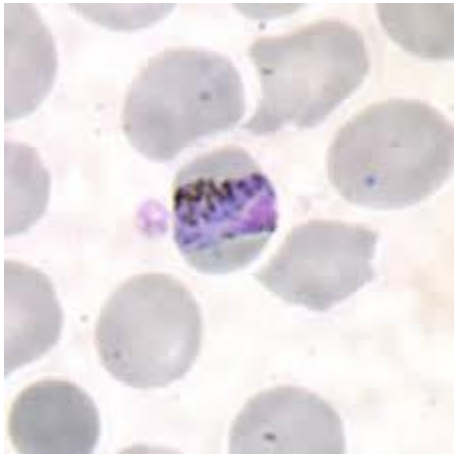


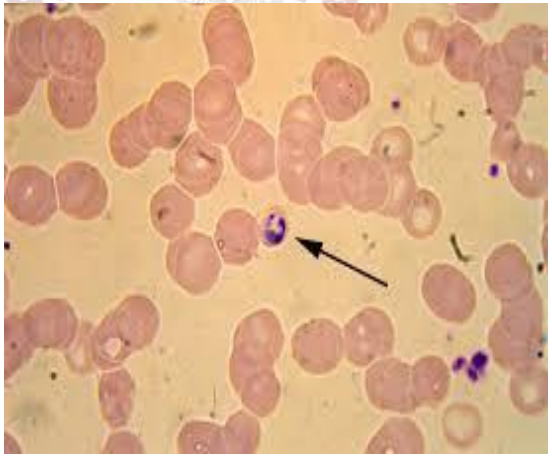


Plasmodium ovale

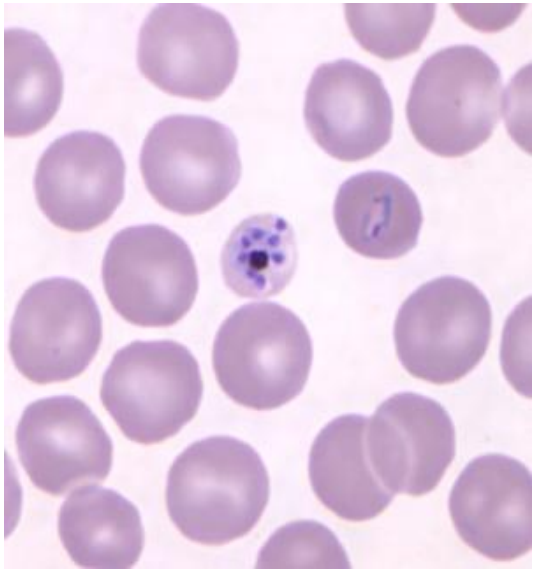


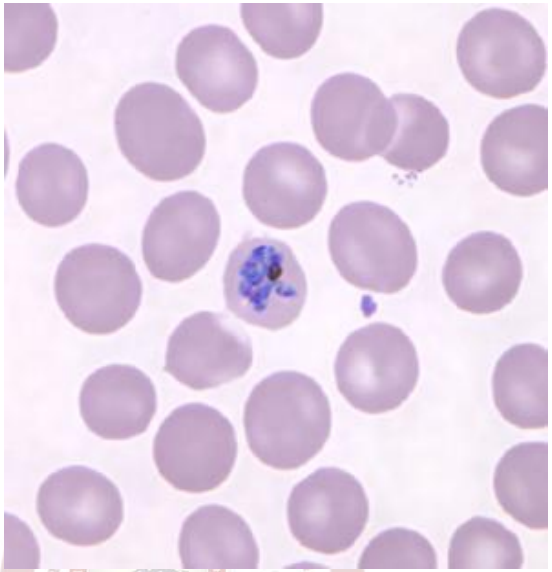


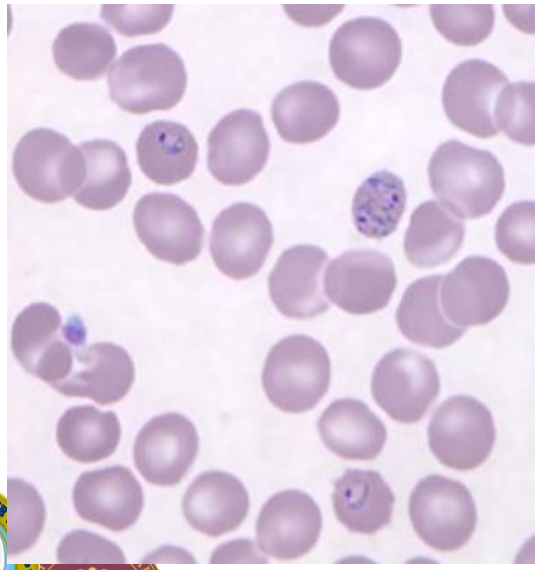


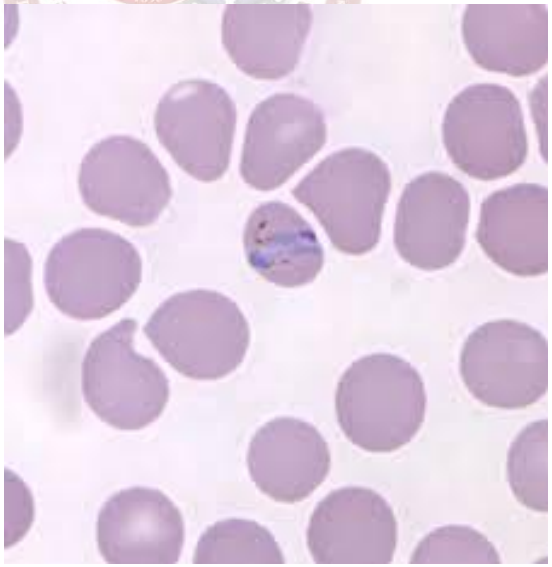


Plasmodium malariae









Plasmodium knowlesi

BinaxNOW® Malaria (Alere, Inc.)

- FDA-cleared rapid (<15 min) diagnostic test
- Non-microscopic
- Single reagent
- Minimally-trained operator
- Environmentally robust
- RDTs will NOT replace malaria microscopy
  - Confirmatory test for species, parasite density
  - Back-up to rule out inaccurate results

Parasite Growth in the Blood

>Log increase in parasites per 48-hour cycle (for *P. falciparum*)

Threshold	Parasitemia	Parasites/ul	Parasite burden
Expert Microscopy	0.0005%	20-50	10^{8} parasites
Symptoms in non-immunes	0.002%	100	10^{9} parasites
Malaria RDT	0.005%	100-1000	$10^{9\text{-}10}$ parasites
Severe malaria	2%	100,000	10^{12} parasites
Death	10%	500,000	10^{13} parasites

Prepatent & Incubation Periods (parasites in detectable in blood by microscopy vs. illness)

Species	Prepatent Period	Incubation Period
P. falciparum	11 - 14 days	8 - 15 days
P. vivax	11 - 15 days	12 - 20 days
P. ovale	14 - 26 days	11 - 16 days
P. malariae	21 - 28 days	18 - 40 days
P. knowlesi	11 days?	10-12 days?

RDT Limitations

- Decreased sensitivity at lower parasitemias
- Temp and humidity both degrade the nitrocellulose strip's ability to transport the blood and buffer solution
- Faint positive test lines can be hard to see
- Cannot split a box when only need small numbers. Sold 25 cards per box, but you only get one bottle of buffer/lysing agent.

BinaxNOW® Sensitivity- *P. falciparum*

Parasitemia (per µL)	Sensitivity
>5000	99.7%
1000-5000	99.2%
500-1000	92.6%
100-500	89.2%
0-100	53.9%
Overall	95.3%
Specificity	94.2%

Official performance data from manufacturer

BinaxNOW® Sensitivity- *P. vivax*

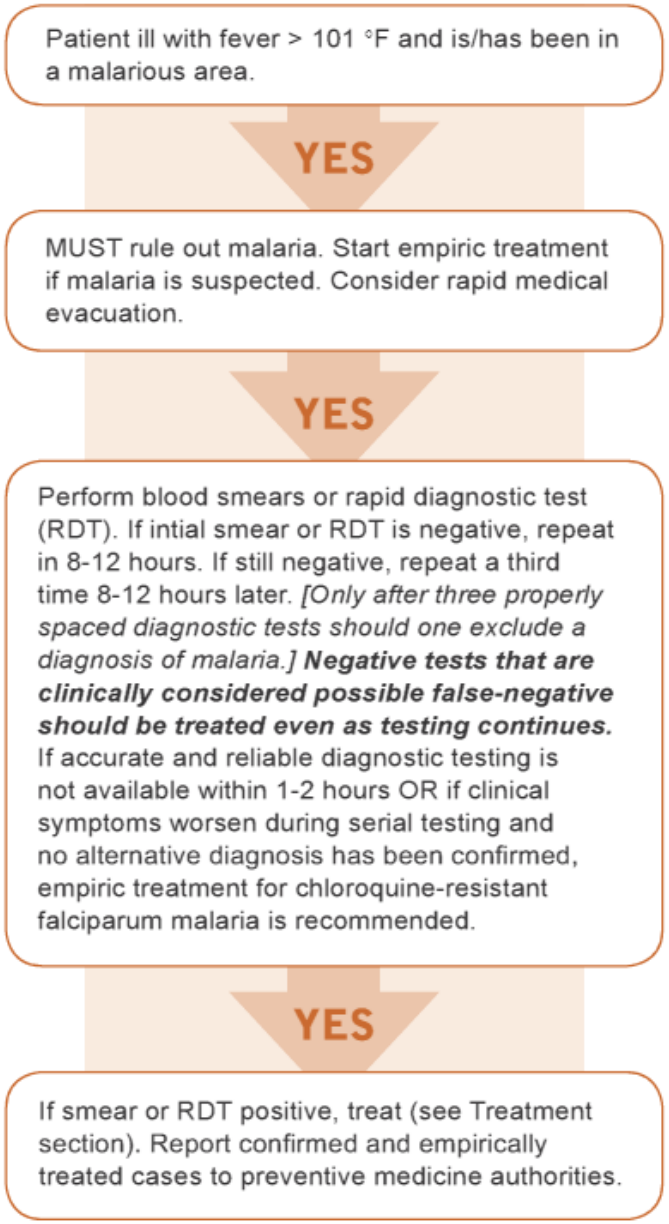
Parasitemia (per µL)	Sensitivity
>5000	93.5%
1000-5000	81.0%
500-1000	47.4%
100-500	23.6%
0-100	6.2%
Overall	68.9%
Specificity	99.8%

Official performance data from manufacturer

"Good doctors are useless without good discipline. More than half the battle against disease is fought not by doctors, but by regimental officers. It is they who see that the daily dose of mepacrine is taken, that shorts are never worn, that shirts are put on and sleeves turned down before sunset. . . I therefore had surprise checks of whole units, every man being examined. If the overall result was less than 95% positive, I sacked the commanding officer. I only had to sack three; by then the rest had got my meaning."

General Slim, Burma Campaign, WW II
(Under General Slim, the malaria rate in troops decreased from 12 per 1,000/day to 1 per 1,000/day)

Treatment Algorithm (TG336)



Particularly non-Pf


ANASTASIS
CORTICIS PERVVIÆ,
SEV
CHINÆ CHINÆ
DEFENSIO,
SEBASTIANI BADI GENVENSIS
Et
Publicæ Sanitatis in Ciuitate Consultoris,
Contra
VENTILATIONES
IOANNIS IACOBI CHIFLETII,
GEMITVSQVE
VOPISCI FORTVNATI PLEMPII,
Illustrium Medicorum.
ILLVSTRISSIMO D.
IOANNI LVCÆ DVRATIO

Source: gallica.bnf.fr

- **Jesuit's Bark**, due to alkaloids, is the most celebrated specific remedy for all forms of malaria. It is obtained from several species of the genus Cinchona, of the order Rubiaceae
- **1630: Countess Chinchon**, the wife of Spanish Viceroy, was saved from terminal malaria by bark powders recommended by the Jesuits of Saint Paul's College in Lima, Peru
- **1632: Jesuit Barnabe' de Cobo** (1582-1657) rendered important services in the exploration of Mexico and Peru. In his capacity of procurator of the Peruvian province of his order, he brought the bark from Lima to Spain, and afterwards to Rome and other parts of Italy

Roles of Antimalarial Drugs

	Prophylaxis	Anti-relapse (Pv or Po liver stage)	Treatment (asexual blood stage)	Anti-transmission (gametocyte/ sporogony)
Primaquine	Yes	Yes	No	Yes
Tafenaquine	Yes	Yes	Yes	Yes
Artemisins	No	No	Yes	Yes
Halofantrine	No	No	Yes	No
Fansidar	No	No	Yes	No
Quinine	No	No	Yes	No
Atov/prog	Yes	No	Yes	Maybe
Chloroquine	Yes	No	Yes	No
Doxycycline	Yes	No	Yes	No
Mefloquine	Yes	No	Yes	No

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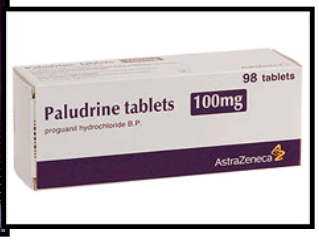
Plasmodium falciparum becomes Resistant to Antimalarial Drugs- Continuous New Drug Development and Licensure is Required

Drug	Introduced	First Reported Resistance	Difference (Years)
Quinine	1632	1910	278
**Chloroquine	1945	1957	12
**Proguanil	1948	1949	1
**Sulfadoxine-pyrimethamine	1967	1967	0
**Mefloquine	1977	1982	5
**Malarone	1997	2002	5

****WRAIR support for US FDA approval**

Quinine

Chloroquine



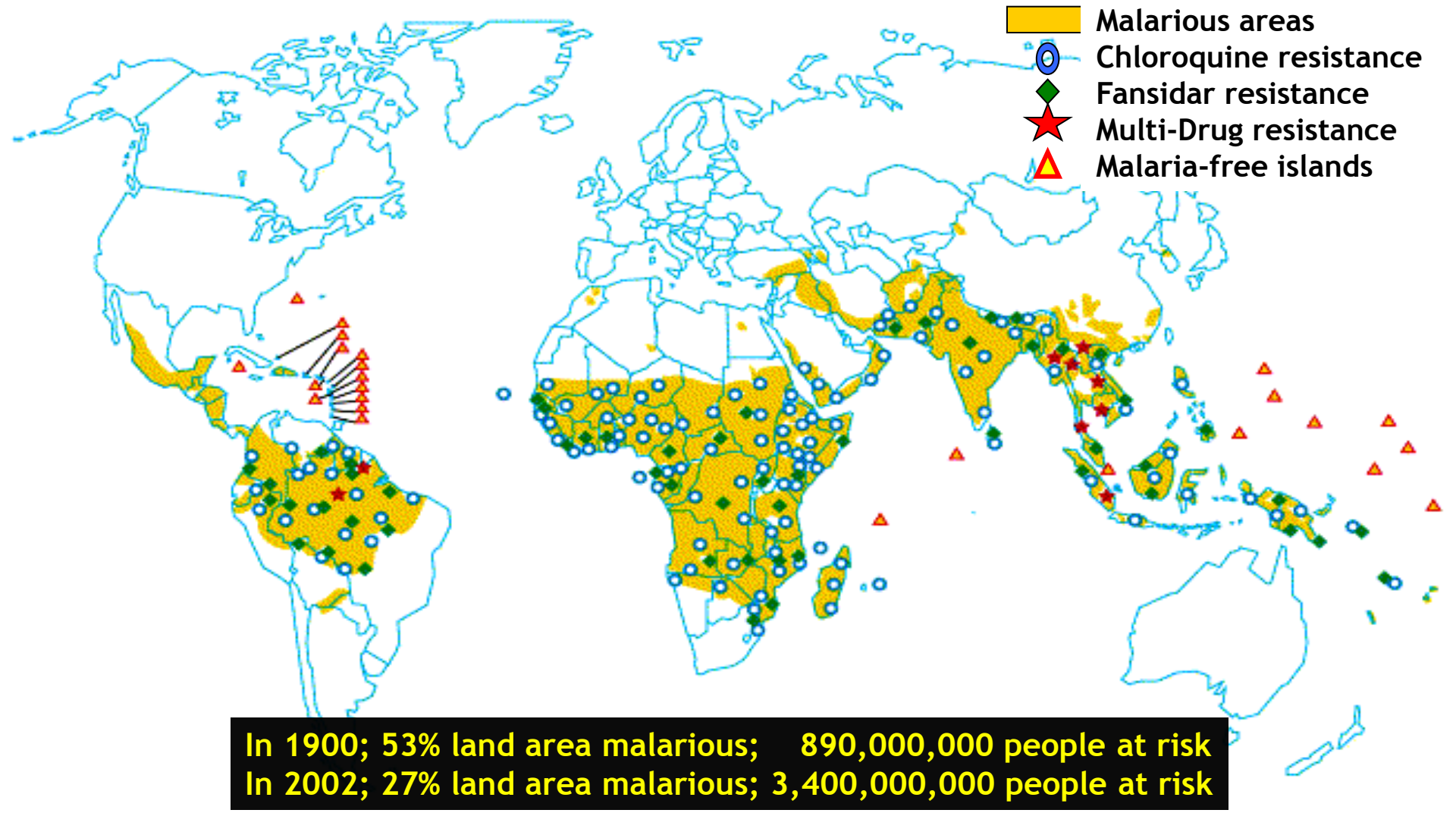
Proguanil

Fansidar

Mefloquine

Malarone

Multi-Drug Resistant *P. falciparum* Malaria Means that Effective Drugs are not Affordable



In 1900; 53% land area malarious; 890,000,000 people at risk
In 2002; 27% land area malarious; 3,400,000,000 people at risk

Wongsrichanalai C et al. Epidemiology of Drug-Resistant Malaria Lancet Inf Dis 2002;2:209-218.

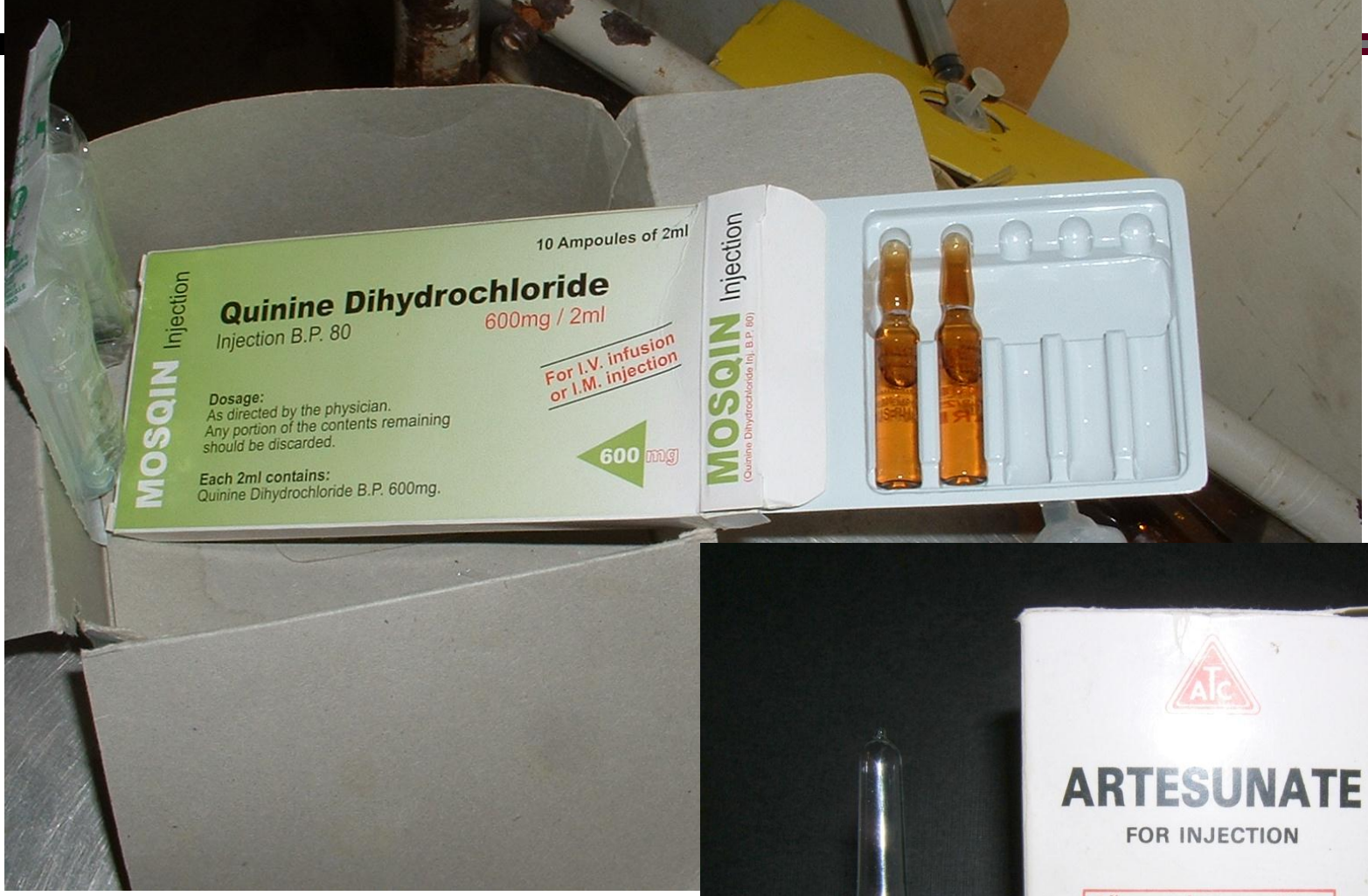
Malaria Treatment (Adult doses)

- **Intravenous treatment of severe malaria**
  - Quinidine gluconate:
    - Load with 10 mg/kg in 250 cc over 1-2 hours
    - Maintenance dose of 0.2 mg/kg/min for 72 hours
  - Artesunate (**treatment IND**): 2.4 mg/kg at 0, 12, 24, 48, and 72 hours
- **Oral treatment of uncomplicated *P. falciparum* malaria**
  - Proguanil / atovaquone (Malarone®): 4 tabs daily for 3 days
  - **Artemether-lumefantrine (Coartem®):**
    - 4 tabs x 1, followed by 4 tabs at 8 hours, then 4 tabs twice daily for 2 days (6 total doses)
  - Quinine sulfate + doxy or PS
  - Mefloquine (Lariam®): 1250 mg (5 tabs) x 1
  - Chloroquine (Aralen®): (**DO NOT USE IN AFRICA OR ASIA)**
    - 1 gram (600 mg base) loading dose
    - 500 mg (300 mg base) in 8 hours, 24 hours, and 48 hours
- **Available and can be used (Rx adjuncts)**
  - Doxycycline, clindamycin, azithromycin
- **Radical cure of relapsing malaria**
  - Chloroquine + primaquine

Oral vs. Intravenous Treatment

- Parasitemia >5%
- Unable to tolerate oral medications
- Signs of end-organ damage
  - Renal failure
  - Pulmonary edema/respiratory failure
  - Coma
  - Severe anemia (transfusion)

If yes to any of the above, then IV



Source: Kent Kester

CDC's Compassionate Use IND

- WRAIR produced 1,000 vials of the "clinical lot" for compassionate use IV Artesunate (AS)
- CDC has a Compassionate Use IND for IV AS
  - Compassionate Use IND went into effect on 21 June 2007
  - Complete cross-reference to U.S. Army IND for IV AS
  - Administered by Domestic Response Unit & Malaria Branch
  - Announcement Made on 03 August 2007 in MMWR

- Now released to Canadians, and will be made available in Australia, EU, and elsewhere

  -Forward supply located at LRMC

DRUG	PROBLEMS
Artemisinin	Recrudescence, Neurotoxicity
Atovaquone	Resistance
Azithromycin	Limited efficacy
Chloroquine	Resistance
Doxycycline	Phototoxicity, GI intolerance
Fansidar	Resistance, Allergic Rxns
Halofantrine	Cardiotoxicity
Mefloquine	Resistance, Psychiatric effects
Primaquine	Narrow Therapeutic Index
Proguanil	Resistance, Mouth ulcers
Quinidine gluconate	Going off the market?
Quinine	Resistance, Tinnitus

Evidence of Artemisinin-Resistant Malaria in Western Cambodia

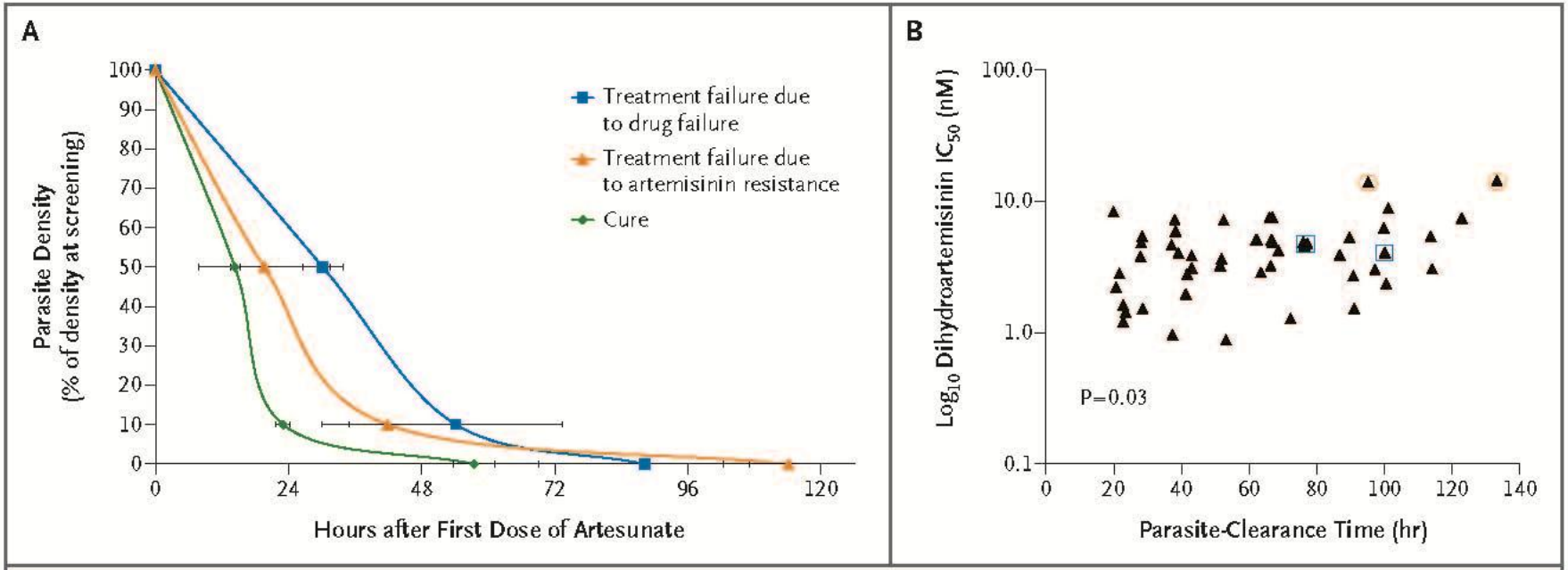


Figure 1. Parasite Density, Parasite-Clearance Time, and 50% Inhibitory Concentration (IC_{50}) among Patients Receiving Artesunate, According to Clinical Outcome.

Panel A shows the parasite-reduction curves for the 56 patients who were cured, the 2 patients classified as having artemisinin-resistant infections, and the 2 with drug failures (i.e., patients who had recrudescence but who were not classified as having artemisinin-resistant infection, since the drug level was inadequate). The data points and horizontal I bars denote the means and standard errors. Panel B shows the parasite-clearance times in the artesunate group, as compared with the IC_{50} for dihydroartemisinin ($R=0.31$, $P=0.03$). Orange circles indicate patients whose infection was classified as artemisinin-resistant, and blue squares patients in whom treatment failed but whose infection was not classified as resistant.

NEJM 359;24 11Dec08 2619

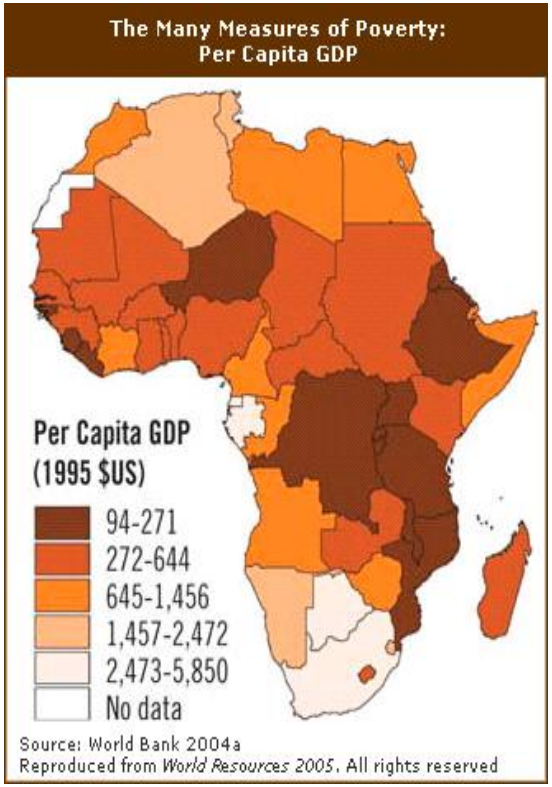
Prevention

- Avoid outbreaks
  - ?Realistic, given mission
- Awareness of peak exposure times/places
  - Night-feeders, geographic distribution
- Appropriate clothing
  - Long-sleeved shirts, long pants, boots, and hats
- Bed nets
- Insecticides
  - DEET, Picaridin, OLE/PMD (Repel, Off!), IR3535 (Skin So Soft Bug Guard Plus Expedition and SkinSmart).
- Chemoprophylaxis
- Vaccines

Figure: Pregnant woman sitting in front of her long-lasting insecticide treated net

Sources: theguardian.com
Childrensprize.org

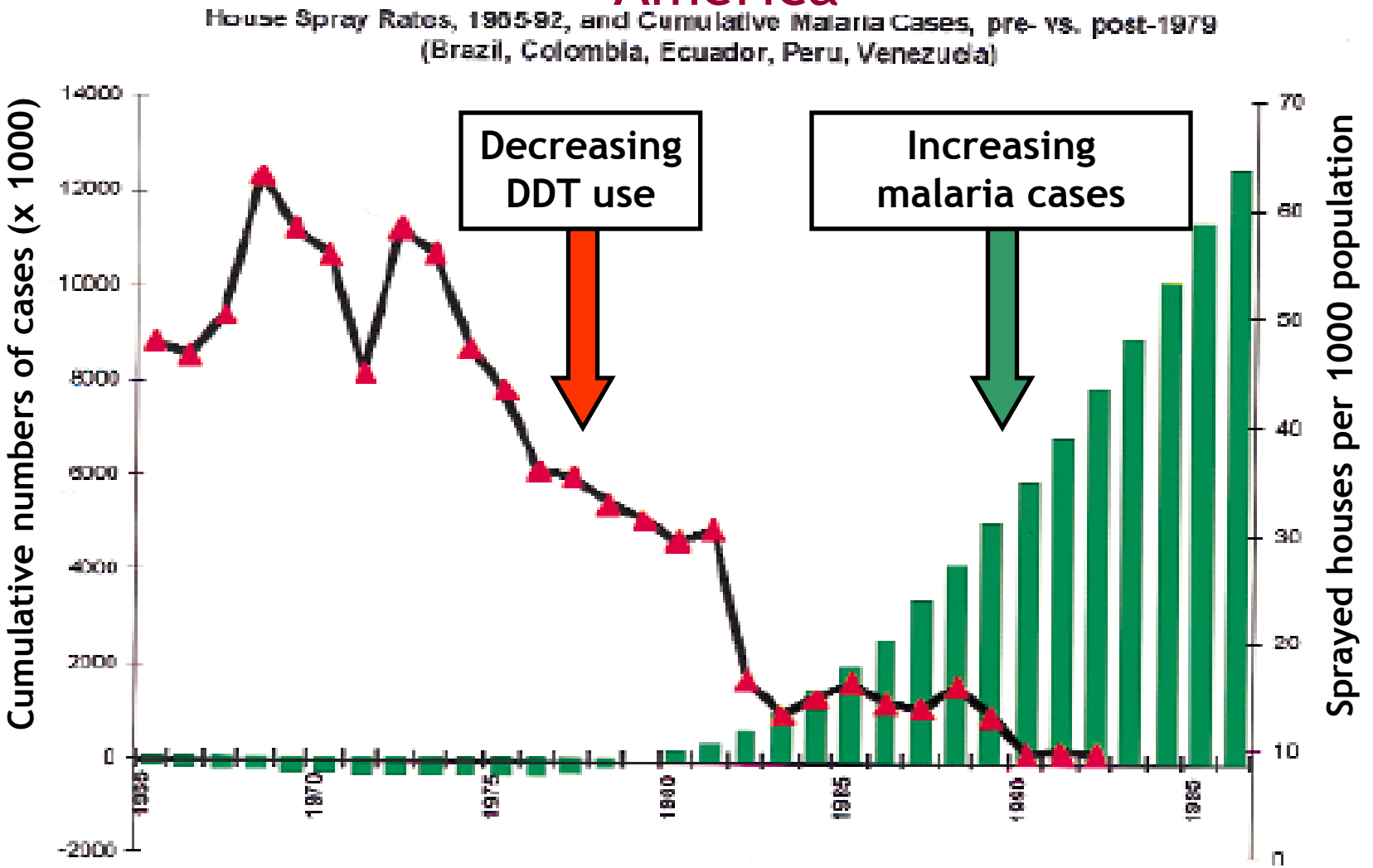
ITNs – Insecticide Treated Nets



Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004;(2):CD000363.

- ITNs versus no nets // protective effect
  - 50% reduction in malaria attacks
  - 45% reduction in severe malaria attack
  - 17% reduction in death
- Additional benefits
  - Improved maternal health & hematocrits
  - Improved infant health & birth weights
- Cost: ~$6
- Cost effective: Yes
- Usage: Less than 10% of children at risk
- Issues:
  - Too expensive for poor users to purchase
  - Requires retreatment with insecticide
  - Requires repair
  - Requires education to promote use

Indoor Residual Spraying (IRS)
DDT Use and Cumulative Malaria Cases in South America



Attaran A et al. Balancing risks on the backs of the poor. Nature Medicine 2000;6:279-280

Chemoprophylaxis

- Consulting for traveler
  - Can do anything that works.
  - Traveler can take medical advice, or not.
- Force Health Protection
  - Prescribed meds must have FDA indication for use
  - Malaria Chemoprophylaxis limited to 3 meds
    - Doxy
    - Mefloquine
    - Malarone

Source: CAPT Claggett, USN

Chemoprophylaxis

Drug	Tablet Size	Dose	Start (pre-deploy)	Stop (re-deploy)	Disadvantages	Pregnancy
Malarone (Atovaquone/ Proguanil)	250mg/100mg	One tablet daily	1-2 days	7 days	Expensive, no if Cr Cl <30 ml/min, must be taken with food	No
Doxycycline	100mg	100mg daily	1-2 days	4 weeks	Photosensitivity, gastritis/esophagitis (must give with liquid, full stomach, upright for 30 minutes), vaginitis	No
Mefloquine	250mg	250mg weekly	3 wks preferable, 1-2 OK	4 weeks	Resistance in SE Asia, Black box for depression/neurotoxicity, cardiac conduction abnormalities	Yes
Chloroquine	500mg (300mg base)	500mg weekly	1 week	4 weeks	Resistance, pruritus in dark-skinned persons, rare blood dyscrasias, psoriasis, hx of psychosis, prolonged QT, rare retinopathy	Yes
Primaquine	26.3mg (15mg base)	30mg base	1 day	7 days	G6PD, food (gastric irritation), methemoglobinemia	No
Primaquine	26.3mg (15mg base)	30mg base	Protection against late relapse Pv/Po	Total of 14 days (6mg/kg total dose)	G6PD, food (gastric irritation), methemoglobinemia	No

Adapted from Freedman D, NEJM 2008

Chemoprophylaxis

- Malarone
- Doxycycline
- Mefloquine-if you can't tolerate the first 2 and not in SE Asia
- Chloroquine-few areas where Pf is sensitive
- Primaquine-short duration

Table 1. Relative Risk of Malaria among Travelers, 2000 through 2002.*

Region Visited	Relative Risk (95% CI)
Very-low-risk area†	1.0
Caribbean	3.8 (1.9–7.5)
North Africa	6.9 (3.6–13.3)
South America	8.3 (4.9–13.9)
Southeast Asia	11.5 (8.3–15.9)
Central America	37.8 (24.0–59.6)
South Asia	53.8 (37.4–77.4)
Oceania	76.7 (50.8–115.9)
Sub-Saharan Africa	207.6 (164.7–261.8)

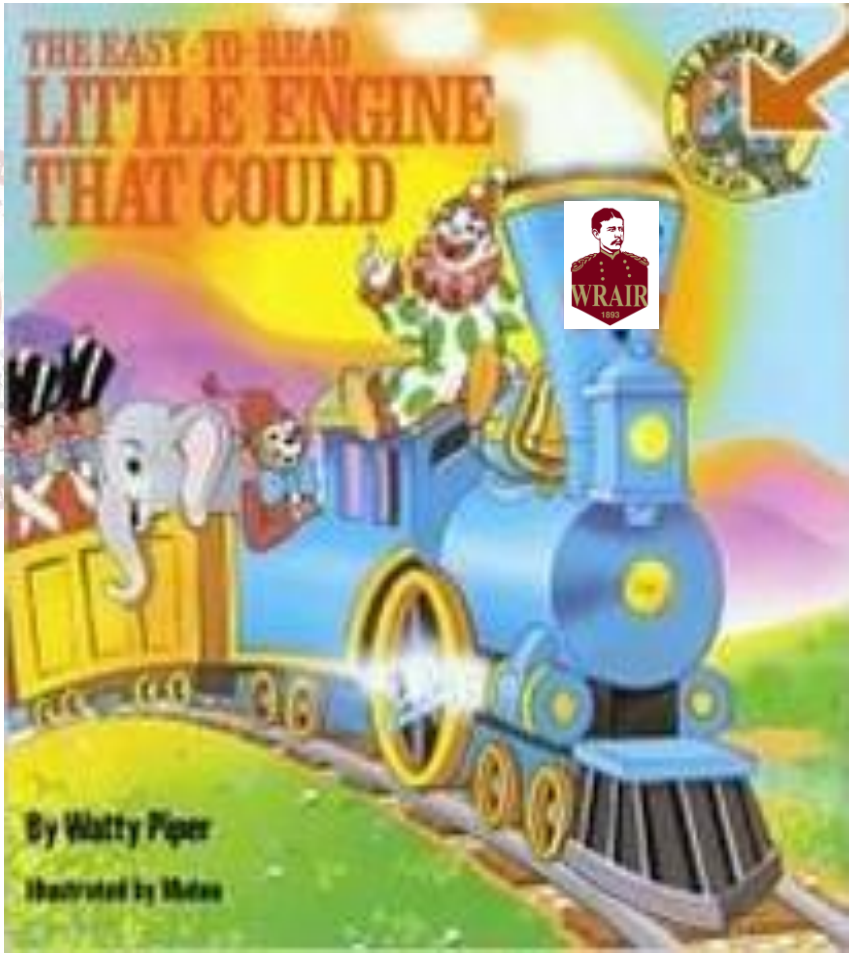
* Approximate relative risks were based on 1140 cases of malaria among travelers in the GeoSentinel database, with areas visited as numerators and tourist arrivals in that region (according to World Tourism Organization data) as estimates for denominators. Adapted from Leder et al.[12]

† Very-low-risk areas were Europe, Northeast Asia, Australia, New Zealand, North America, and the Middle East.

Source: NEJM

DoD Antimalarial Drug Program
The Biggest Little Drug Company in the World

- Filed 63 IND's with US FDA
  - Chloroquine
  - Primaquine
  - C-P Tablets
  - Mefloquine
  - Doxycline
  - Halofantrine
  - Fansidar
  - Malarone
  - IV Artesunate



Vaccines

- No licensed vaccines yet
- RTS,S/AS01
  - Glaxo-Smith-Kline (GSK) + PATH Malaria Vaccine Initiative (MVI)
  - Specific for *P. falciparum*
  - Recently completed Phase 3 trials
    - 11 sites: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania.
    - 15,460 infants and young children
    - 2 cohorts: infants (6-14 weeks; receive 3 doses of vaccine at 6, 10, 14 weeks with normal childhood vaccines); 5-17 month olds

Final results from a large-scale Phase III trial of the RTS,S malaria vaccine candidate

Vaccines

- Results (efficacy)
  - 5-17 months at first immunization: 55% reduction of all malaria, 47% reduction against severe malaria over 12 months
  - 6-14 weeks: 33% (all malaria), 37% (severe malaria) over 12 months
  - 5-17 months (after 18 months follow up): 40-77%, 11/11 sites
  - 6-14 weeks (after 18 months follow up): 40-77%, 4/11 sites
  - Post booster (0,1,2,20 months schedule) at 18 months
    - 5-17 months: 36% (all malaria), 32% (severe malaria, anemia, malaria hospitalizations, all-cause hospitalizations)
    - 6-14 weeks (0,1,2 month schedule) at 18 months: 18%
      - With month 20: 26%
      - Severe malaria: 0%

Controversies in Malaria

- **Prophylaxis… drug to use?**
  - Mefloquine (probably not) vs. Malarone vs. Doxycycline
- **Prophylaxis… to do or not?**
  - Short-term vs. Long-term Deployments
- **Prophylaxis… duration?**
  - Continuous vs. Interrupted
- **RDTs…**

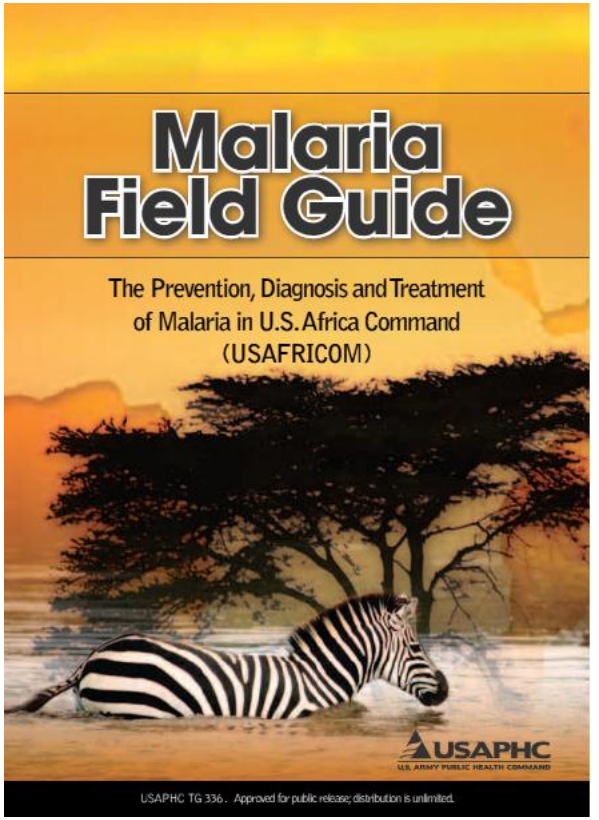
Malaria Take Home Points

- Malaria continues to evolve, not just in resistance, but in new species
- Malaria is as important a consideration for force health protection today as ever
- Malaria is not just a force health protection issue, but a strategic stability operations consideration in the global war on terrorism
- We have more tools today than ever, but we can lose them at any time and we must understand and respect their limitations

Fighting Malaria

- Requires expensive, sustained efforts
- Medical facilities are not equipped to quickly and accurately diagnose and effectively treat malaria
- Effective control efforts if subsidized and applied
  - Indoor Residual Spraying (IRS) with DDT - saves lives
  - Insecticide Treated Bed Nets (ITNs) - save lives
  - Artemisinin combinations treatment – saves lives
  - Improved diagnosis – use expensive drugs for those that need it
  - World is waiting for a malaria vaccine
- Eradication requires multiples efforts and multiple solutions

QUESTIONS?

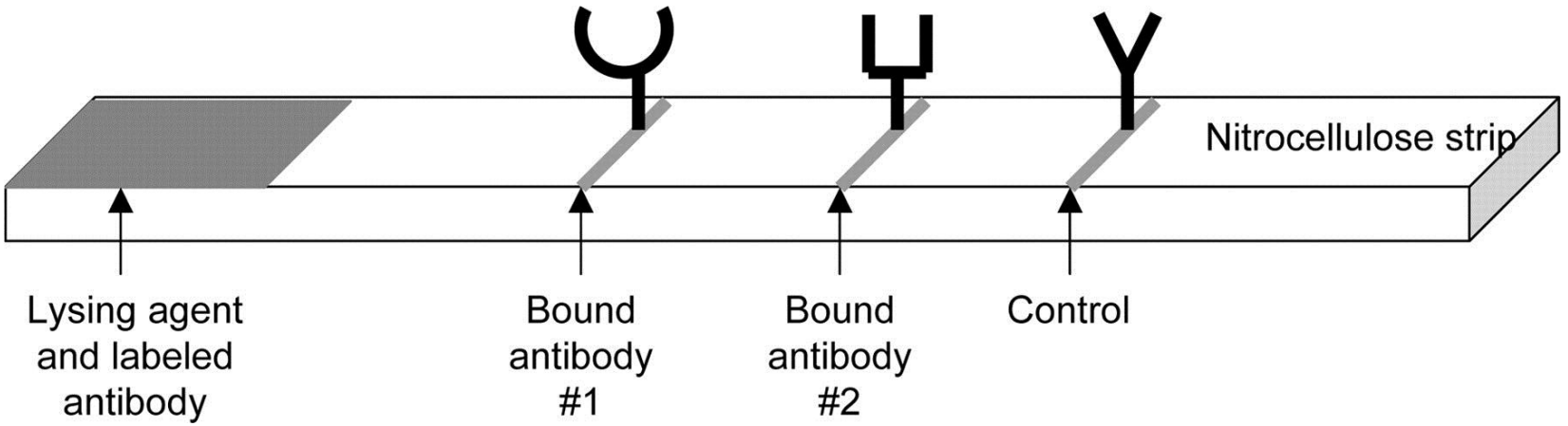


USAPHC TG 336

Rapid Diagnostic Tests

- FDA cleared
  - BinaxNow® Malaria, Alere
- Reliability
  - False negatives – Prozone Effect
  - Hyperparasitemia – too much antigen
  - HRP-2 assays (16/17) most affected; pLDH and aldolase not affected
- Follow-up
  - FDA ‘clearance’ Labeling – what does it actually say? (need for microscopy confirmation)

Schematic of an MRDT. On one end of the nitrocellulose strip, one or two indicator-labeled antibodies, one specific for each target antigen, are placed.



Murray C K et al. Clin. Microbiol. Rev. 2008;21:97-110